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EDITORIAL

Michel Foucault in the 21st Century: his influence on academic integrity

Michel Foucault en el siglo XXI: su influencia en la integridad académica

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Paul-Michel Foucault was known as Michel Foucault. His father, Paul Foucault, was a distinguished surgeon; his mother, Anne Malapert, came from a family with a medical tradition. He was the second of three children: Francine Foucault (older sister) and Denys Foucault (younger brother).

This year marks the 100th anniversary of the birth of Michel Foucault, who was born on October 15, 1926, in Poitiers, France, and passed away on June 25, 1984. He held degrees in philosophy, psychology, and history, specializing in psychopathology and experimental psychology. He worked at various French institutions, such as the *École Normale Supérieure*, as well as institutions abroad, achieving international recognition while holding the Chair of the History of Systems of Thought at the *Collège de France*. His work focused on the historical analysis of the ways in which societies produce knowledge, establish norms, and exercise mechanisms of control over individuals. Rather than a closed theory, he developed a critical methodology centered on the relationships between knowledge and power within modern institutions.

Among his major contributions, his studies on madness, medicine, the human sciences, the prison, and sexuality stand out. Works such as "*History of Madness*," "*The Birth of the Clinic*," "*The Order of Things*," "*The History of Sexuality*" transformed contemporary thought by demonstrating that knowledge does not emerge in a neutral or isolated manner, but rather within specific historical, cultural, and institutional structures. However, many authors consider his most influential work to be "*Discipline and Punish: The Birth of the Prison*," where he analyzes the evolution of modern disciplinary systems and describes how schools, hospitals, barracks, and prisons develop mechanisms for the surveillance, assessment, and normalization of behavior; we address these latter concepts in the context of contemporary education in the following paragraphs.

Key concepts from Foucault's work in contemporary education

Foucault's relevance to contemporary education lies precisely in his analysis of educational institutions as spaces for both knowledge production and social regulation. From his perspective, every educational institution establishes criteria defining which knowledge is valid, who may exercise the authority of knowledge, and how the ethical behaviors of society's future professionals are shaped; in other words, educational institutions enact the *theory of power*, which generally posits that "*where there is power, there is resistance.*" Consequently, *disciplinary* mechanisms are applied to regulate and control the behavior and conduct of individuals as members of the system; rather than employing direct physical violence, this regulation operates subtly. Compliance with discipline is verified through *surveillance* – a process that goes beyond mere watching or spying. Surveillance is a structured, asymmetrical technique of power – a panoptic system – wherein

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the observer must watch everything, yet the observed never know the precise moment they are being watched. The observer classifies and corrects; the observed become obedient, internalize the control, and ultimately come to police themselves. Together, these elements enforce *normalization*, establishing a distinction between "normal" (acceptable) behavior and "deviant" (unacceptable) behavior.

Furthermore, all educational institutions establish norms, rules, and behavioral patterns that impose standards of conduct, appearance, thought, and values; failure to comply results in corrective measures. To meet these established standards, educational institutions employ *training* techniques, drill individuals, and mold behaviors; they utilize set schedules and spaces and may incorporate rewards, punishments, repetitive exercises, and other mechanisms to achieve their objectives. This training acts directly on bodies (individuals) to render them simultaneously docile – easy to subdue and transform – and useful – productive. It does not seek to destroy the body, but rather to maximize its capabilities while neutralizing its potential to question.

Foucault's philosophy distinguishes between *knowledge* and understanding; *knowledge* is the product of dynamic power relations and historical and cultural structures, social hierarchies, and specific institutions; therefore, it does not emerge in a neutral or isolated manner. He conceived as a social and cultural construct that is constantly changing and dispute (depending on who holds power).

Understanding – understood as the body of knowledge and techniques developed within a specific field, such as medicine, psychology, or various areas of healthcare – always entails an ethical dimension, as it influences how individuals understand reality and act upon it.

Application of Foucault's work to healthcare personnel and academic integrity

Healthcare personnel comprise a diverse group that may include physicians, nurses, dentists, psychologists, nutritionists, and optometrists, among others. Their goal is to maintain physical, mental, and social well-being; they prevent disease, promote healthy lifestyles, and provide the tools necessary for making sound decisions and managing daily life. Their work involves teaching and learning processes, as well as dialogue – both among colleagues and with patients. Consequently, the training of healthcare personnel is extensive and must be guided by the principles of academic integrity – honesty, trust, respect, fairness, and responsibility. While these principles remain constant across institutions, the methods of application and enforcement vary.

From an administrative standpoint, various guidelines, laws, and regulations exist to govern the interactions of all members and ensure order, safety, justice, and well-being. Examples include the organic law, standard contracts, codes of conduct, best practice manuals, and official standards. These measures serve to guarantee order rather than merely monitor behavior, and they apply consequences to actions rather than simply imposing punishment. While it is true that disciplinary methods differ from those used in the past – reflecting societal changes, technological advancements, and evolving human needs – the systems governing us (such as norms and regulations) must also change, update, and adapt to prevent and resolve contemporary issues.

In education, we must start from the premise that education is not neutral, as the teacher holds "power" and exerts influence through knowledge and discipline. In the classroom, the teacher manages grades and maintains discipline; by employing negotiation and debate, the teacher encourages students to question and participate actively, rather than imposing authority through force or fear. Shifting away from an authoritarian stance allows the teacher to move from a power based on control to one that is democratic and transformative – without losing that power.

While the course is conducted with academic freedom, there must be a syllabus outlining the start and end of the course and a method for assessing the knowledge acquired. The professor must update their classes and tailor them to the specific needs and skills of each student group. The use of modern tools – such as artificial intelligence (AI) – should not be demonized; they simply exist and can serve to support learning in various ways, ranging from generating images and summaries to implementing virtual tutors.

At the start of each course, the instructor outlines the assessment method and must be transparent regarding the evaluation criteria (clearly indicating what is permitted, acceptable similarity percentages in written work, the use of AI, among other factors); they must also foster self-assessment and peer assessment to move away from exclusive control. This should not be confused with fostering docile bodies or obedient individuals who accept rules almost naturally or automatically.

Instead, discussion, questioning, and negotiation should be encouraged.

The professor can improve the classroom environment by fostering student participation, integrating teams, and adjusting the physical seating arrangement – such as placing tables in a circle rather than in rows – while also using a tone of voice that alters hierarchical power dynamics. In online classes, it is important to maintain student engagement through interactive lessons, address individuals by name, encourage participation, and prevent distraction.

Students apply power theory by questioning classroom authority dynamics, asking genuine questions rather than merely repeating the teacher's words, and rejecting the notion of absolute truths handed down by the instructor; meanwhile, teachers may be willing to negotiate, accept criticism, and use dialogue to transform the learning process. This enables students to shift from being passive subjects of obedience to becoming active agents characterized by critical thinking and constructive resistance.

The student actively participates in the construction of knowledge – spanning both theoretical and practical acquisition – by proposing changes to class dynamics and seeking out current information; they view the classroom as a space for sharing and expanding knowledge rather than a place where things are imposed. The student makes decisions regarding their own learning and assumes responsibilities, such as proposing and discussing topics and working in teams.

The priority placed on – and interest in – obtaining a qualification, a degree, a professional license, or membership in medical councils, societies, or groups serves as a labor market regulation mechanism that confers reputation, yet it is a consequence of acquiring knowledge.

In scientific research, the researcher exercises power by defining the problem, selecting the sample, and interpreting the data. At the same time, they must recognize that the subjects under study are not mere objects, but rather co-creators of knowledge. Knowledge is power, and scientists legitimize certain truths in order to continue their research and, eventually, apply their findings. In the professional sphere, researchers compete for scientific capital, funding, prestige, and the opportunity to innovate. Academic integrity applies at every stage of the research process.

Discussion

Michel Foucault transformed the understanding of knowledge, power, and institutions. To this day, his intellectual work continues to offer indispensable conceptual elements for analyzing the ethical and educational challenges facing contemporary society, particularly regarding health education and academic integrity. The training of physicians, nurses, dentists, and other healthcare professionals depends on the rigorous acquisition of scientific knowledge and the development of ethical competencies focused on patient well-being.

Academic dishonesty – such as copying classmates' assignments, lifting text from the internet, using others' schoolwork, using ideas without attribution, copying articles, or submitting plagiarized theses – is a matter of public concern in Mexico. However, the word "*plagiarism*" is not explicitly defined or legally codified in Mexican penal codes or general statutes. Instead, the Federal Penal Code regulates copyright and intellectual property; specifically, Title Twenty-Six ("Crimes Regarding Copyright") establishes criminal penalties for actions such as the reproduction, publication, or use of others' works – willfully and for profit – without proper authorization. When such infractions occur in an academic setting, they are handled internally by each institution through university regulations, institutional tribunals, or committees tasked with determining the appropriate resolution and consequences. These consequences can range from a formal reprimand to the revocation of awarded degrees.

Regarding the use of AI, various educational institutions employ it in diverse processes – such as administering online admission exams and conducting medical research and diagnostics – making it contradictory to prohibit students from using it. Furthermore, there is generative AI, which, as the name implies, creates original, new content; it is widely used by educators to produce supporting images and videos. It is worth noting that this technology requires precise user instructions and learns from the creation patterns employed in each instance, enabling it to predict patterns and generate unique results. Foucault's theory is relevant here, as it posits that we are not passive subjects defined by obedience but rather individuals capable of critical thinking; consequently, it is possible to promote the responsible use of these tools and encourage the establishment of institutional guidelines aligned with national and international standards.

A serious form of dishonesty involving the fabrication and falsification of data has been documented in health research. Fabrication entails inventing data or results – creating non-existent information or adding fictitious bibliographic sources – and presenting them as real,

often with the aim of aligning them with a hypothesis. Falsification involves changing or manipulating data, modifying records, altering samples and processes, or citing sources that were neither read nor used; the objective here is to distort the truth of the research. Publisher who detects this practice retract the articles; however, the resulting damage is both short- and long-term, ranging from the erosion of trust in science to the stalling of research progress. When an article is retracted, the publisher assumes the role "surveillance and punishment," while authors are relegated to a passive role, unaware of when they are being scrutinized. Consequently, before engaging in such dishonest practices, authors should bear in mind that scientific techniques and science itself are neutral.

Another form of dishonesty is honorary – or courtesy – authorship, which involves listing a person as an author who made no actual contribution to the study. The motives vary, ranging from agreements to boost a group's publication count or the repayment of favors, to lending weight and prestige to the publication by including a renowned figure in the field. This practice often appears alongside "ghost authorship," which conceals the true creator of the knowledge – the researcher who actually performed the work. It represents an abuse of the trust placed in young, inexperienced researchers; believing that "this is how you start" or that one must "pay one's dues," they often accept the situation without resistance. In his essay, "*What Is an Author?*", Foucault explains the author's role regarding a text's value, the weight of intellectual property, and the invisible hierarchies exercised by the principal investigator; it is within this context that the resistance of subordinates – or "docile bodies" – finds its rationale.

Just as authors can commit acts of dishonesty, so too can publishers; predatory publications charge high article processing charges but lack editorial quality controls and peer review, and offer rapid turnaround times between submission and acceptance, as their goal is financial profit rather than the dissemination of science. The researcher trusts the publisher due to the speed of response, the persistent mass invitation emails, and metrics – such as high impact factors and journal rankings – that are actually fabricated. Authors suspend their critical judgment regarding these traps; compounded by the pressure to publish, they become compliant subjects who internalize their worth based on factors such as publication counts and citation numbers. The pressure to publish – known as "publish or perish" – is imposed by the system, which grants authority in each field based on the number of publications; consequently, the status of a faculty member who conducts research differs from that of a standard faculty member. Researchers who stop publishing for any reason lose credibility, reinforcing the norm that a higher volume of publications equates to being a better researcher. If a researcher engages in academic resistance and refuses to publish, they receive poor evaluations and see their project funding reduced or eliminated.

To prevent the previously described instances of dishonesty, institutions have established ethics and research commissions and/or committees. These bodies perform various functions – such as evaluating, guiding, and overseeing scientific projects to ensure methodological rigor, safeguarding participant confidentiality, preventing conflicts of interest, and fostering transparency in data management. Their role extends beyond mere surveillance and sanctioning; they operate within a structured framework featuring rotating membership, and members receive specific training for their roles. Researchers prepare protocols in accordance with the standards set by the institution and the committee – effectively internalizing the committee's oversight – resulting in a panoptic practice where everyone monitors one another. There is no physical threat involved; rather, the scope of the protocol, the timeline, and the infrastructure required to carry it out are monitored. If a criterion is not met, the committees do not issue a direct ban; instead, they provide guidance and may make the research subject to certain conditions. When a breach of academic integrity is detected, the committee reviews and analyzes the case – hearing from the parties involved to determine the severity of the infraction based on institutional regulations (combining hierarchical oversight with documentary record-keeping) – and ultimately issues a decision regarding corrective action or sanctions, thereby functioning as an instrument of disciplinary and normalizing power.

Surveillance and punishment of dishonest practices throughout professional training and practice will prevent clinical errors and inappropriate decisions that affect people's health. Academic integrity, therefore, represents not only a university value but also a fundamental requirement for ensuring the quality of healthcare.

Reflection from a Foucaultian perspective

How does generative AI transform the relationships between knowledge, power, and academic integrity?

First, generative AI is a non-neutral technological tool; this is because the algorithm it uses to arrive at knowledge depends not only on the data with which it was fed – direct results of human research – but also on training and data selection criteria that enable it to identify predictive statistical patterns. The generated information mimics data validated through traditional scientific rigor, creating an illusion of objective truth without actual verification. The role of the author is lost, as there is no human effort involved in creating the text – let alone conducting experiments – leaving no author to cite in references. Students justify using generative AI to enhance their learning; yet, even if they use it to avoid intellectual effort, they are clearly not the authors – so, does this constitute academic dishonesty? Institutions should regulate its use rather than ban it; this does not mean seeking a centralized legal prohibition, but rather unraveling how algorithms operate as a mechanism of knowledge and power. Power is exercised by the professor through the surveillance of the student, yet the use of generative AI – by bypassing plagiarism detectors – renders traditional disciplinary methods obsolete.

These are times of collaboration, and healthcare students must not only understand theory but also put it into practice – engaging their senses and internalizing knowledge so it can be applied to patient care. Both educators and students must recognize that the flow of knowledge is bidirectional, and that generative AI is shifting academic power dynamics; the exchange between professor and student is essential for scientific progress, requiring both parties to assume their respective responsibilities.

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ORIGINAL ARTICLE

Implementation of an integrated laboratory workflow for pulmonary histoplasmosis diagnosis in a Mexican tertiary-care hospital

Implementación de un flujo de trabajo integrado de laboratorio para el diagnóstico de la histoplasmosis pulmonar en un hospital de tercer nivel mexicano

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Abstract

Background: *Histoplasmosis is a systemic fungal infection caused by the Histoplasma complex, endemic in regions of the Americas, including southern Mexico. Although it is the most common endemic mycosis, it remains underdiagnosed, particularly among patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), leading to increased morbidity and mortality. Timely diagnosis is essential.* **Objectives:** *The objective of this study is to describe the implementation of an integrated laboratory workflow for the diagnosis of pulmonary histoplasmosis in a tertiary-care hospital.* **Method:** *A bronchoalveolar lavage sample was analyzed, including differential testing for respiratory pathogens. Direct examination with potassium hydroxide, Giemsa staining, culture on Sabouraud dextrose agar, and urinary antigen detection using an enzyme immunoassay were performed.* **Results:** *Differential tests were negative. Extracellular and intracellular yeast within macrophages were observed. Urinary antigen testing was positive, confirming the diagnosis. Culture showed typical Histoplasma characteristics.* **Conclusion:** *The combined use of rapid and conventional diagnostic techniques enables timely identification of histoplasmosis, particularly in immunocompromised patients.*

Keywords: *Histoplasma capsulatum. HIV/AIDS. Histoplasmosis.*

Resumen

Antecedentes: *La histoplasmosis es una infección fúngica sistémica causada por el complejo Histoplasma, endémica en regiones de América como el sur de México. Aunque es la micosis endémica más frecuente, sigue siendo subdiagnosticada, especialmente en pacientes con VIH/SIDA, lo que incrementa la morbilidad y mortalidad. El diagnóstico oportuno es fundamental.* **Objetivos:** *El objetivo de este estudio es describir la implementación de un flujo de trabajo de laboratorio integrado*

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para el diagnóstico de histoplasmosis pulmonar en un hospital de tercer nivel. **Método:** *Se analizó un lavado broncoalveolar con pruebas diferenciales para patógenos respiratorios. Se realizaron examen directo con KOH, tinción de Giemsa, cultivo en agar Sabouraud y detección de antígeno urinario mediante inmunoensayo.* **Resultados:** *Las pruebas diferenciales fueron negativas. Se observaron levaduras extracelulares e intracelulares en macrofagos. El antígeno urinario fue positivo, confirmando el diagnóstico. El cultivo mostró características típicas de Histoplasma.* **Conclusión:** *El uso combinado de técnicas diagnósticas rápidas y convencionales permite una identificación oportuna de la histoplasmosis, especialmente en pacientes inmunocomprometidos.*

Palabras clave: *Histoplasma capsulatum. VIH/SIDA. Histoplasmosis.*

Introduction

Histoplasmosis is a fungal disease caused by members of the *Histoplasma* species complex, a group of thermally dimorphic fungi distributed throughout the Americas, Africa, and other endemic regions.[1,2] In Mexico, states, such as Campeche, Tabasco, and Chiapas are considered endemic, but there are other states, such as Veracruz, Guerrero, Morelos, San Luis Potosí, Nuevo León, and Tamaulipas where this fungal disease also occurs.[3] Although this mycotic disease is considered cosmopolitan and the most common endemic pulmonary/systemic mycosis, it is also an underdiagnosed disease.[2,3] This fungal infection is acquired through the inhalation or inoculation of macroconidia or aleuroconidia. This disease is particularly linked to activities, such as cave exploration and exposure to guano, but it can also be acquired through exposure to soil contaminated with bird droppings.[4] Exposure to this dimorphic fungus may be asymptomatic in most immunocompetent individuals. However, in certain cases, a mild to moderate pulmonary infection develops, characterized by fever, headache, myalgia, cough, and chest pain, a clinical picture that often leads healthcare professionals to initially consider community-acquired pneumonia.[5] The clinical manifestation and severity of the disease depend on multiple factors, including the host's immune status, the extent of exposure to the inoculum, and genetic susceptibility to mycoses.[1] According to the latest data from The Joint United Nations Program on human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS),[6] an estimated 40.8 million people (37.0-45.6 million) were living with HIV worldwide in 2024. During that same year, approximately 1.3 million people (1.00-1.7 million) became infected, demonstrating that, despite medical advances, the epidemic continues to pose a global public health challenge. In terms of mortality, approximately 630,000 people (490,000-820,000) died from AIDS-related illnesses. However, access to treatment has shown considerable progress: 31.6 million people (27.8-32.9 million) received antiretroviral therapy in 2024, a key indicator in reducing deaths and improving the quality of life of those living with HIV. Since the beginning of the epidemic, the cumulative figures reveal the magnitude of the impact: an estimated 91.4 million people (73.4-116.4 million) have acquired HIV, and 44.1 million (37.6-53.4 million) have lost their lives to AIDS-related illnesses. In Mexico, approximately 400,040 people were living with HIV, with nearly 28,000 newly reported cases during the same period. Opportunistic fungal infections remain a major cause of morbidity and mortality among immunocompromised patients.[6,7] The HIV pandemic and the bacterial/fungal infections associated with this viral infection are causing health systems to modify their diagnostic algorithms, particularly to provide accurate results. Cryptococcosis is one of the most common fungal infections in HIV patients; however, infections, such as histoplasmosis should not be overlooked and should be included in diagnostic algorithms in non-endemic areas.[7] The objective of this study is to describe the implementation of an integrated laboratory workflow for the diagnosis of pulmonary histoplasmosis in a tertiary-care hospital.

Materials and methods

Sample reception and differential diagnosis

On July 9, 2025, a bronchoalveolar lavage (BAL) sample was received at the mycology laboratory of the Research Division for the diagnosis of fungal infections in a newly diagnosed HIV patient with signs and symptoms of pulmonary infection. BAL specimen was homogenized by gentle mixing and centrifuged at 3,000 rmp for 10 min. The supernatant was discarded, and the resulting sediment was used for direct microscopic examination with 20% potassium hydroxide (KOH), Giemsa staining, and fungal culture. No mucolytic treatment was applied before processing.

Before mycological investigation, differential diagnostic testing for respiratory pathogens was performed bacteriology and molecular diagnostics. Conventional bacterial cultures were used for the detection of *Staphylococcus aureus* and *Streptococcus pneumoniae*, molecular testing included GeneXpert® (Cepheid, Sunnyvale, CA, USA) for *Mycobacterium tuberculosis*, real-time reverse transcription-polymerase chain reaction (PCR) for SARS-CoV-2 using primers and protocols recommended by the World Health Organization (WHO), FilmArray® multiplex PCR testing (BioFire Diagnostics, Salt Lake City, UT, USA) for the detection of *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila*, and the VIASURE *Pneumocystis jirovecii* Real Time PCR Detection Kit (CerTest Biotec, Zaragoza, Spain) for *P. jirovecii*.

Biosafety

The sample was handled using personal protective equipment (gown, gloves, KN95 mask, protective face shield) in a Class II biological safety cabinet (BSC). Before and after handling the sample, the cabinet was subjected to ultraviolet (UV) irradiation, and cleaning and disinfection procedures were performed using 1.5% sodium hypochlorite. The laboratory was additionally disinfected for 30 min using UV-C irradiation towers from the Helios system (Surfacide, Waukesha, WI, USA) and sodium hypochlorite at the same concentration described above. The cultures derived from the diagnosis were inactivated with 10% formaldehyde for tube culture and by moist heat at 121°C, 15 psi, for at least 30 min for Petri dish culture.

Mycological diagnosis

Cryptococcus-screening

Cryptococcal capsular antigen (CrAg) was detected in serum samples using the Cryptococcal Antigen Lateral Flow Assay (CrAg® LFA; IMMY, Norman, OK, USA) according to the manufacturer's instructions. Briefly, 40 μL of serum was mixed with one drop of the assay diluent provided in the kit, and the lateral flow test strip was inserted into the mixture. The reaction was incubated at room temperature for 10 min before visual interpretation. A positive result was defined by the presence of both the control and test lines, whereas the presence of the control line alone was interpreted as a negative result. All assays were performed under standardized laboratory conditions, and internal quality control procedures recommended by the manufacturer were followed to ensure assay validity.

Diagnosis of pulmonary mycosis

BAL samples were processed according to the laboratory's routine diagnostic procedures. Direct microscopic examination was performed using 20% KOH preparations and Giemsa staining.

Culture and microscopic observation of *Histoplasma capsulatum*

The culture was performed in Sabouraud Dextrose Agar (SDA) medium on a plate for the description of macroscopic morphology and in a tube for microscopic examination. The cultures were incubated at 25°C ± 2 for 14 days.

For microscopic examination, the culture in the tube was previously inactivated with 10% formaldehyde, followed by staining with erythrosine to observe the typical structures of this dimorphic fungus.

Immunological tests for the diagnosis of histoplasmosis

When pulmonary infection by *H. capsulatum* was suspected based on Giemsa staining, Urinary *Histoplasma* antigen detection was performed using the Clarus *Histoplasma* Galactomannan enzyme immunoassay (EIA) (IMMY, Norman, OK, USA) according to the manufacturer's instructions using the cutoff calibrator procedure. Microplate absorbance was measured at 450 nm with a reference wavelength of 620/630 nm. Corrected optical density (OD) values were obtained by subtracting the absorbance of the blank well from the absorbance of each sample and control. EIA Units were calculated using the manufacturer's equation:

$$EIA\ units = \frac{Corrected\ OD\ of\ the\ sample}{Corrected\ OD\ of\ the\ 12.5\ ng/mL\ cutoff\ calibrator} \times 10$$

According to the manufacturer's criteria, results < 1.0 EIA Units were considered negative, whereas results ≥ 1.0 EIA Units were considered positive. Assay validity was confirmed by including the blank, the 12.5 ng/mL cutoff calibrator, and the positive and negative controls in each assay run. In addition, a 25 ng/mL standard was included as an internal quality-control measure to

verify assay performance, although it was not used for calculation of EIA Units.

Results

Differential diagnosis

The tests performed for differential diagnosis by classical microbiology and molecular biology methods of the most common infections associated with the lower respiratory tract were negative (Table 1).

Mycological diagnosis

Serum CrAg testing using the Cryptococcal Antigen Lateral Flow Assay (CrAg® LFA) was negative. Direct examination of the BAL specimen with 20% KOH revealed the presence of blastoconidia (Fig. 1A), while Giemsa staining demonstrated intracellular yeasts measuring 1-3 μm within macrophages (Fig. 1B). These microscopic findings supported the presence of a fungal pathogen in the lower respiratory tract despite the negative serum cryptococcal antigen result.

Confirmation of histoplasmosis by enzyme immunoassay

Urinary *Histoplasma* antigen detection using the Clarus® *Histoplasma* Galactomannan EIA (HGM-EIA, IMMY, USA) yielded an OD450 of 2.244. Using the manufacturer's cutoff calibrator procedure, the sample corresponded to 39.73 EIA Units, well above the positivity threshold of 1.0 EIA Units (Fig. 2).

Macroscopic and microscopic morphology of H. capsulatum

In SDA culture medium, *H. capsulatum* developed semi-hairy colonies (Fig. 3A). The colonies were initially grayish-white in color, with a tendency to have a denser center and a loose periphery. The edges were irregular and diffuse, with mycelial projections toward the periphery. Over time, the colonies showed a progressive change to brown or ochre tones on their surface.

Direct examination with erythrosine (Fig. 3B) revealed the presence of septate, thin, smooth-walled hyphae. From these, characteristic conidial structures were observed: small, rounded, sessile microconidia distributed laterally on the hyphae, and thick-walled, tuberculate macroconidia with digitiform projections on their surface, spherical in morphology and larger in size.

Table 1. Differential diagnosis of pulmonary infection in a human immunodeficiency virus-positive patient

Differential diagnosis	Result
Mycobacterium tuberculosis	Negative
Mycoplasma pneumoniae	Negative
Streptococcus pneumoniae	Negative
Haemophilus influenzae	Negative
Staphylococcus aureus	Negative
Legionella pneumophila	Negative
SARS-CoV-2	Negative
Pneumocystis jirovecii	Negative

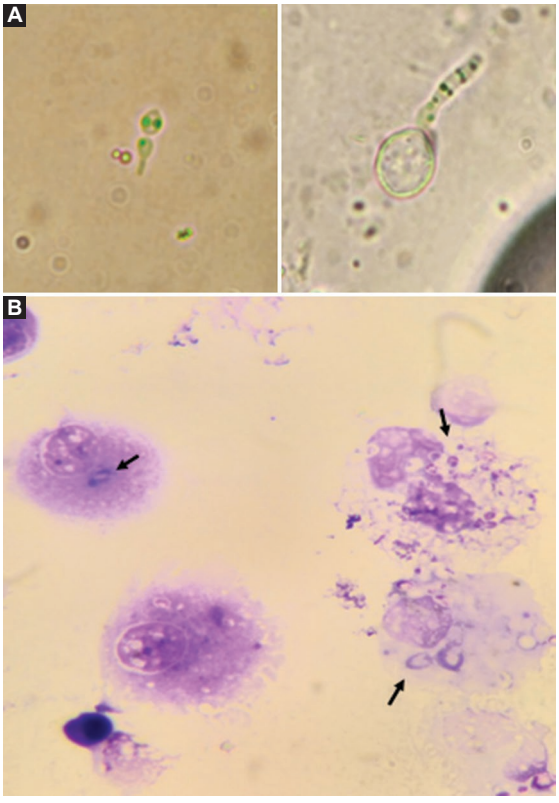

Figure 1. Direct examination and Giemsa staining of bronchoalveolar lavage. **A**: extracellular yeast are observed. **B:** intracellular yeasts are observed present in macrophages.

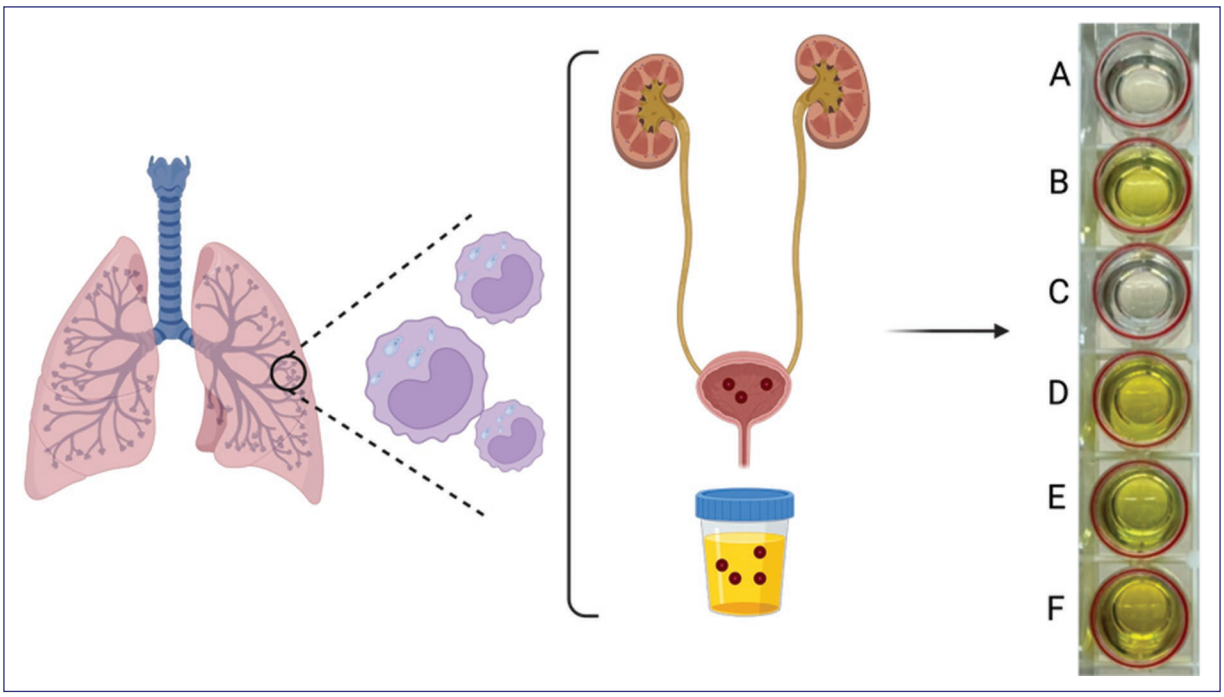

Figure 2. Detection of *Histoplasma* antigen in urine using an immunoenzymatic assay. **A:** blank. **B:** positive control. **C:** negative control. **D**: 25 ng/mL analytical control. **E:** 12.5 ng/mL cutoff calibrator. **F:** urine sample.

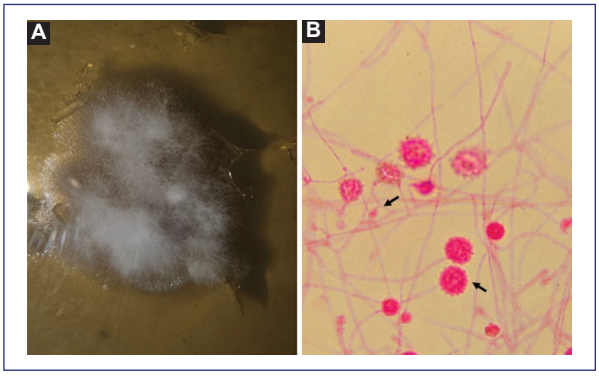

Figure 3. Macroscopic and microscopic morphology of *Histoplasma capsulatum*. **A:** macroscopic morphology. **B:** microscopic morphology, typical aleuroconidia, and macroconidia in a "corcholata" shape are observed.

Discussion

HIV infection progressively compromises cellular immunity and, if untreated or inadequately treated, may progress to AIDS. This stage is defined by the presence of specific AIDS-defining conditions, irrespective of the CD4+ T-cell count.[8] These conditions are primarily opportunistic infections and include tuberculosis, mycobacterial infections, *P. jirovecii* pneumonia, candidiasis, *Salmonella* septicemia, extrapulmonary or disseminated coccidioidomycosis, histoplasmosis, and cryptococcosis, including cryptococcal meningitis.[8] The lung has been identified as the organ most frequently affected in patients with HIV/AIDS, and respiratory infections continue to be one of the leading causes of morbidity and mortality in this population.[9] Throughout the course of the infection, most patients develop pulmonary complications, predominantly of infectious etiology.[10,11] At present, in developed countries, the most prevalent pulmonary complication is bacterial pneumonia, predominantly pneumococcal pneumonia, followed by *P. jirovecii* pneumonia and tuberculosis.[9,12] However, other fungi besides *P. jirovecii* can also cause pulmonary infections in HIV-positive patients,[13] such as *Cryptococcus* spp., *Aspergillus* spp, and *Histoplasma* spp.[14-16] In Latin America, histoplasmosis is a common infection, and it is estimated that around 30% of HIV/AIDS patients diagnosed with this disease die as a result of it.[13] Although this disease is endemic, the diagnosis of histoplasmosis can be delayed, coupled with the fact that *Histoplasma* antigen detection or PCR are not always available and classical mycology, specifically the gold standard of culture, is slow and insensitive.[17,18] In this study, *H. capsulatum* was detected in an HIV-positive patient through the implementation of immunoenzymatic tests and

classical mycology. Before the sample arrived at the mycology laboratory of the research division, clinicians investigated the most common bacterial, viral, and mycobacterial causes of pulmonary infection using culture and molecular methods[13,19] (Table 1). Given the suspicion of a fungal infection of etiology other than *P. jirovecii*, a diagnosis was first made using classical mycology alongside immunoenzymatic techniques (Fig. 1). Direct examination revealed the presence of free yeast, although direct examination with KOH is not a diagnostic technique for histoplasmosis. Based on the suspicion of a fungal infection of unknown etiology, this examination was performed as a screening test to search for fungi other than *H. capsulatum*. The Giemsa stain gave us a diagnostic clue when intracellular blastoconidia were observed in macrophages. Although stains are not the gold standard, in our case, the Giemsa stain was very useful as a diagnostic technique. The rapid confirmation obtained with urinary antigen detection in this study is consistent with present international recommendations, which recognize this assay as the preferred non-culture diagnostic method for people living with advanced HIV because it allows diagnosis several days before culture results become available while maintaining excellent diagnostic performance (Fig. 2). The culture was positive after 13 days, which was confirmed by microscopic observation of structures characteristic of this fungus (Fig. 3). Diagnosing histoplasmosis is a challenge for health systems.[20] A multidisciplinary approach and the implementation of sensitive and rapid diagnostic techniques are very important for providing fast and accurate results.[21] The diagnosis of histoplasmosis in immunocompromised patients relies on a combination of conventional and non-culture-based methods, each with variable performance depending on the clinical context. Fungal culture remains the gold standard due to its high specificity; however, it is limited by long turnaround times and reduced sensitivity, particularly in localized disease.[22] Direct microscopy and cytopathology can provide rapid presumptive diagnosis, especially when intracellular yeasts are identified within macrophages, although their sensitivity is operator-dependent.[23] Antigen detection assays in urine and serum have emerged as highly valuable diagnostic tools, particularly in patients with advanced HIV infection. Urine antigen testing has demonstrated high sensitivity, exceeding 90% in disseminated histoplasmosis, making it especially useful in severely immunocompromised patients.[21] Molecular methods, such as PCR offer rapid and specific detection; however, their availability remains limited in many settings, and standardization is still evolving.[18]

In this study, the integration of direct microscopy, antigen detection, and culture allowed for timely and accurate diagnosis, highlighting the importance of a multimodal diagnostic approach. Although histoplasmosis was not initially suspected in this patient, the unexpected observation of intracellular yeast-like organisms on Giemsa staining prompted targeted testing for *Histoplasma* and ultimately led to rapid diagnosis by urinary antigen detection. This finding exposed an important gap in our institutional diagnostic workflow. Present IDSA and the WHO guidelines recommend *Histoplasma* antigen detection as a first-line diagnostic assay for people living with advanced HIV in whom histoplasmosis is clinically suspected, particularly those at risk for disseminated disease, because of its high diagnostic sensitivity and its ability to substantially shorten the time to diagnosis compared with conventional culture.[24-26] In response to these recommendations and the diagnostic experience gained from the present case, urinary *Histoplasma* antigen detection has now been incorporated into our institutional diagnostic algorithm for the routine evaluation of people living with advanced HIV undergoing investigation for opportunistic infections. This strategy is intended to facilitate earlier recognition of histoplasmosis, reduce diagnostic delays, and improve timely access to appropriate antifungal therapy in a population at high risk of severe disease. This work highlights the need to strengthen diagnostic algorithms in Mexican healthcare settings. The implementation of algorithms in non-endemic areas is of utmost importance, as it has been reported that climate change has led to an expansion in the distribution of *Histoplasma* spp., posing a challenge for regions where the diagnosis of this fungus is not part of routine testing.[27] The diagnostic workflow described in this report reflects present clinical recommendations for the evaluation of pulmonary infections in immunocompromised patients, in which common bacterial, viral, mycobacterial, and fungal pathogens must be systematically excluded. This approach may be particularly valuable in non-endemic settings, where histoplasmosis is often not included in the initial differential diagnosis.

Conclusions

This study illustrates how the integration of differential microbiological testing, direct microscopy, *Histoplasma* antigen detection, and fungal culture can facilitate the timely diagnosis of pulmonary histoplasmosis in immunocompromised patients.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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BRIEF REVIEW

Quality assessment of cataract surgery results

Valoración de la calidad de los resultados de la cirugía de catarata

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Abstract

Evaluation of quality in cataract surgery requires more than finding any improvement in vision. The first variable to analyze is post-operative corrected visual acuity, which should allow the patient to conduct daily activities. Provided that this visual acuity is good, other factors like post-operative recovery time, quality of life, and economic evaluations may help to improve the quality of cataract surgery. These topics require evaluation both in centers with a low volume of surgeries, and in surgical campaigns that cover many patients. This document highlights relevant aspects of the referred variables, and deals with the opportunity of setting quality indicators, which would allow the generation of continuous information for improving quality in cataract surgery.

Keywords: *Best corrected visual acuity. Cataract. Cataract surgery. Phacoemulsification. Quality. Quality of life.*

Resumen

La evaluación de la calidad en la cirugía de catarata requiere algo más que la simple mejora de la visión. La primera variable a analizar es la agudeza visual corregida postoperatoria, la cual debe permitir al paciente realizar sus actividades diarias. Siempre que esta agudeza visual sea adecuada, otros factores como el tiempo de recuperación postoperatoria, la calidad de vida y las evaluaciones económicas pueden contribuir a mejorar la calidad de la cirugía de catarata. Estos temas requieren ser evaluados tanto en centros con bajo volumen de cirugías como en campañas quirúrgicas que atienden a un gran número de pacientes. Este documento destaca aspectos relevantes de dichas variables y aborda la oportunidad de establecer indicadores de calidad que permitan generar información continua para la mejora de la calidad en la cirugía de catarata.

Palabras clave: *Agudeza visual mejor corregida. Catarata. Cirugía de catarata. Facoemulsificación. Calidad. Calidad de vida.*

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Introduction

Cataracts alter the lens transparency, reduce visual acuity, and according to the World Health Organization (WHO), are the most frequent cause of visual impairment (33%) after uncorrected refractive errors (43%). The only treatment to restore vision in patients with cataract is surgery, which removes the opaque lens and replaces it with an artificial intraocular lens; cataract surgery is the most common surgical procedure worldwide.

At present, the most common method to remove cataracts is phacoemulsification with intraocular lens implantation, a minimally invasive technique that offers an early recovery and allows the patient to restart everyday activities soon. Besides, most cases require no perioperative hospitalization, which gives the procedure an excellent cost-effectivity ratio; a substantial proportion of patients improve their visual acuity after cataract surgery, but evaluating quality in this procedure includes other aspects that may go unnoticed and under-registered (Table 1). This narrative revision deals with variables that could help to evaluate quality in cataract surgery, in addition to an expected visual result.

Table 1. Factors that can modify the outcome after cataract surgery

Pre-operative
Intraocular lens power calculation
Retinal and optic nerve comorbidities
Lens opacity level
Intraoperative
Surgical complications
Surgery time
Post-operative
Follow-up facilities
Attachment to follow-up
Compliance with post-operative care
Post-operative recovery time
Availability of unscheduled post-operative emergency visits
Residual refraction

Visual result after cataract surgery

A study from the United States reported best corrected visual acuity (BCVA) ≥ 20/40 in 93.2% of patients, 1 month after cataract surgery,[1] while an Indian study reported 93.4%.[2] Studies from our country found a mean BCVA of 0.36[3] logarithm of the minimal angle of resolution (log MAR, 20/45, n = 23) and 0.20 log MAR (20/30, n = 156)[4] 1 month after phacoemulsification; a study from Costa Rica reported a visual acuity ≥ 20/40 in 86.8% of their patients 1 month after surgery (n = 2,407).[5]

Patients with monofocal intraocular lenses need a new spectacle prescription for near vision, and sometimes for distance vision, after surgery; completing visual rehabilitation requires waiting for refractive stability, 2-4 weeks after phacoemulsification.

Beyond BCVA, secondary results such as contrast sensitivity, dysphotopsias, performance in low illuminated conditions, and real-life outcomes like accident-related injuries and coordination are critical for perceiving surgical success. There is a reduced rate of falls and driving accidents in older adults after cataract surgery; however, there are still challenges like dysphotopsias and the debate about using lenses with a blue light filter.[6]

At a population level, socioeconomic contexts condition both the access to surgery and visual results; a multinational analysis found strong associations between the Human Development Index, the per capita gross domestic product, and cataract surgery coverage, the use of intraocular lenses, and the proportion of eyes with good surgical visual outcome (≥ 20/60). Less developed countries have higher rates of cataract-related blindness and worse surgical results, and these associations persist after adjusting for year, country, and other factors; these findings reinforce the need of measuring not only surgical volume, but the quality of outcomes.[7]

Post-operative recovery time

Early post-operative symptoms may include mild ocular pain, blurred vision, foreign body sensation, tearing, photophobia, itching, and ocular irritation; they decrease or disappear within the 1st week after surgery.[8]

The lens opacity level changes the visual result and the recovery time after surgery; patients with less opaque cataracts have better results from the first 24 h after surgery, because their procedure uses less energy and causes fewer post-operative inflammation. Patients aged ≥ 60 years recover from cataract surgery in 4 to 16 weeks when their systemic condition is stable; proper post-operative care is essential to achieve the best visual results in the shortest time and improve quality of life (QoL).[9,10]

Control of post-operative inflammation is essential to get good visual results and avoid complications such as cystoid macular edema, posterior capsule fibrosis, keratopathy, or uveitis; steroids and non-steroidal

anti-inflammatory drugs are common resources to treat inflammation after cataract surgery. Steroids may increase intraocular pressure and promote infections, so their use during 2 or 3 weeks after surgery needs close supervision.

Post-operative follow-up usually includes 24 h, 1 week, 2 weeks, 4 weeks, and 3 months' visits.[11] The proportion of patients with complications that need another surgery, within the 1st post-operative days, is 0.65%; 74% of those events appear within the first 40 days after surgery.[12] People who undergo extracapsular cataract extraction have rehabilitation periods of up to 12 weeks, because they need a larger surgical incision.[13]

QoL after cataract surgery

Cataract-induced visual loss may progress gradually and limit the patient's independence; untreated cataracts reduce QoL and life expectancy.[14] Therefore, the use of comprehensive cataract surgical services, including diagnoses, treatment referrals, and rehabilitation, is increasing.[15]

The impact of medical interventions on a patient's QoL refers not only to the success of the procedure but to its impact on different areas of life. Until recently, treatment success definition used only medical criteria, and now it considers the impact on the patient's QoL as well. The WHO defines QoL as "an individual's perception of the self-position in life in the context of the culture and value systems in which he/she lives and in relation to goals, expectations, standards, and concerns." QoL is an indicator of treatment success and a measure of the patient's satisfaction with life overall; it is crucial to understand it and bear it in mind when designing treatment plans to effectively improve the patient's well-being.[14]

The subjectivity of individual experiences makes QoL difficult to measure; however, there are tools (scales and survey questionnaires) which can help to collect data and arrange them appropriately; the term "vision-related QoL" (VR-QoL) covers the multifactorial impact of visual function on an individual's overall well-being. The concept includes measurable aspects of visual impairment, such as difficulties in performing vision-related tasks, and its consequences for emotional well-being and social relations; comfort and satisfaction with visual function may affect VR-QoL, which makes the interaction between BCVA and overall QoL a complex one.[16]

One way of measuring QoL in patients with cataracts is assessing their ability to perform daily activities and their level of comfort and satisfaction with life after surgery.[6] Continuous research is necessary to assess QoL in these patients, as it may help improve not only procedures related to the treatment but perioperative and long-term care ones.

There is a positive association between cataract surgery and improved mental and emotional well-being and greater illness acceptance, even a few weeks after surgery, confirmed using different methods and questionnaires. A multi-cohort study by Queirós et al. showed that cataract surgery results associate with minimal complications, which has a positive impact on the patient's QoL.[17] Kuntorini et al. found no difference between the QoL of people with normal vision and that of patients who had their first cataract surgery.[18]

Besides visual acuity, cataract surgery improves functional dimensions that patients value in everyday life. Phacoemulsification increases the scores of VR-QoL (National Eye Institute Visual Function Questionnaire-25 [NEI-VFQ-25]) at 30 days, with particularly marked gains in posterior subcapsular cataracts, which cause a larger pre-operative functional impairment.[19]

Questionnaires may not capture the whole advantage in certain scenarios; although early cataract surgery provides measurable benefits,[20] the total scores of NEI-VFQ-25 might not change because of "best eye" dominance or sociocultural restrictions of the instrument in limited resource environments.[21] It is then important to select context-sensitive metrics and expand the evaluation of BCVA with functional measurements and patient reports.

Cataract surgery improves QoL in patients with comorbidities.[22-26] In cataract patients with myopia VR-QoL is significantly impaired and gets better after surgery, even more than in patients with normal axial lengths.[24] Cataract surgery significantly increases QoL in patients with retinitis pigmentosa[22] as well as in people with age-related macular degeneration and severe visual impairment.[25] Al Habash and Nagshbandi[26] and Yuasa et al.[27] found that QoL in patients with glaucoma rose significantly after cataract surgery alone or combined with minimally invasive glaucoma surgery, where the effect was larger. Li et al. found that monocular patients reported a larger improvement in VR-QoL and more reduction in the level of depression and anxiety than binocular controls.[28]

Cataract surgery is currently one of the most rapidly evolving fields in Ophthalmology, and advances to date

have brought significant benefits in terms of improving patient QoL.[14] Quality evaluation in uncomplicated cataract surgery must start by finding the proportion of patients with a good visual result (Table 2).

Table 2. Variables that can be used to build quality indicators in cataract surgery

Proportion of eyes with post-operative best corrected visual acuity ≥ 20/40
Recovery time
Difference between expected and actual refraction, 1 month after surgery
Post-operative contrast sensitivity
Proportion of eyes with post-operative complications
Quality of life after cataract surgery
Quality-adjusted life years
Social return on investment
Effective cataract surgery coverage

Indicators in cataract surgery

The idea and purpose of quality systems in Medicine is to find areas for improving the results and quality of the procedures; a relevant approach is to adopt indicators that unify and simplify complex medical interventions and create a common base to compare performance and results from different providers.[29-31] An indicator measures or evaluates progress towards achieving a goal; it can be quantitative (number-based) or qualitative (based on descriptions or perceptions). Good visual acuity after cataract surgery depends on factors like an otherwise healthy eye, an adequate surgical procedure, or a suitable spectacle correction of post-operative refraction; patient satisfaction is a subjective variable also related to expectations before surgery (Table 2).[32-34]

Leading causes of post-operative low vision in Aravind Hospitals are intraoperative complications and an inadequate intraocular lens power calculation. It is advisable to detect and evaluate intraoperative complications, reinforce learning after such cases individually, and set practices that improve the quality of an institution, which leads to keeping low complication rates. Recommendations to achieve high precision in calculating intraocular power are renewing measurement devices and training their users in different methods and formulas.[32]

Quality, efficiency, and safety indicators in cataract surgery are: pre and post-operative BCVA, patient satisfaction measured with the VEFQ-25 test, complication rate, efficiency of the procedure, and impact on the patient's QoL;[33] they have evolved with technology, ongoing surgical techniques, and the need to define and set up best medical practices.[32,35] The most common are post-operative BCVA and refractive precision (a deviation > 0.50 diopters from the target refraction); both indicators help to assess performance, detect deviations, and make informed decisions to find the best surgical practices.[31,34] The Physician Quality Reporting Systems from Medicare and Medicaid Centers of cataract surgery use BCVA ≥ 20/40, complications requiring a second surgery within 60 days, and BCVA improvement 90 days after surgery[30]

The WHO has two core indicators in cataract surgery in its Eye Care Indicators Menu: "result of cataract surgery: visual acuity" and "effective coverage of cataract surgery." The first grades visual result as favorable or satisfactory when BCVA is ≥ 20/40 (6/12, log MAR 0.3) and suboptimal when it is < 20/40-20/200 (mild to moderate visual disability); a poor or unsatisfactory result is BCVA < 20/200, which represents severe visual disability.[36]

This indicator is reported as a percentage, which results from a fraction whose numerator is the number of surgeries with satisfactory, suboptimal, or unsatisfactory result, divided by the total number of surgeries.[36]

The indicator "effective coverage of cataract surgery" shows the coverage extent, which seeks that people who need health care receive it with the quality needed to obtain the aimed vision. This information evaluates access to care and quality of cataract care services in a country; it is the proportion of people who have a good visual result (≥ 20/40) after cataract surgery, with respect to people who need cataract surgery.[36-38]

Continuous improvement in cataract surgery requires a commitment to learn from self-experience and from the best reported practices, based on a structured approach and evidence; it is convenient to have indicators that evaluate surgical practices, to learn which areas require strengthening. Each institution should set up inner monitoring and evaluation (internal benchmarking), so that they have specific and directed practices to improve quality of care.[32,35]

Implementing surgical protocols, documenting measurements (BCVA, post-surgical refractive error, complications rate), and monitoring allows to assess the attachment to the best clinical practices in

Ophthalmology; the periodic and systematic report of this information sets a path to seeking continuous improvement solutions, aimed at improving quality in patient care (Fig. 1).

Tools for improving quality

Technological resources make perioperative surveillance of cataract surgery easier; a study from Austria found a higher satisfaction during post-operative care when patients received a telephone follow-up call on the same day of surgery.[39] A study from France found that SMS messages increased the perception of quality and saved time, with respect to phone calls.[40] Tognetto mentions that there are still gaps in using these resources, such as the learning curve in aged patients, and the evaluation of flare and intraocular pressure during mediate follow-up.[41]

Although there are applications designed to check the process of cataract surgery, their use has not improved surgical results.[42] In an Indian study, exchanging experiences for improving quality decreased intraoperative complications and increased the proportion of patients with good visual outcome and post-operative residual refractive error < ± 0.5 diopters.[32]

Artificial intelligence (AI) based systems for post-operative monitoring are currently under evaluation; their main limitation is that they cannot be generalized.[43] Training AI to evaluate quality in cataract surgery will require reliable, high-quality information.[44]

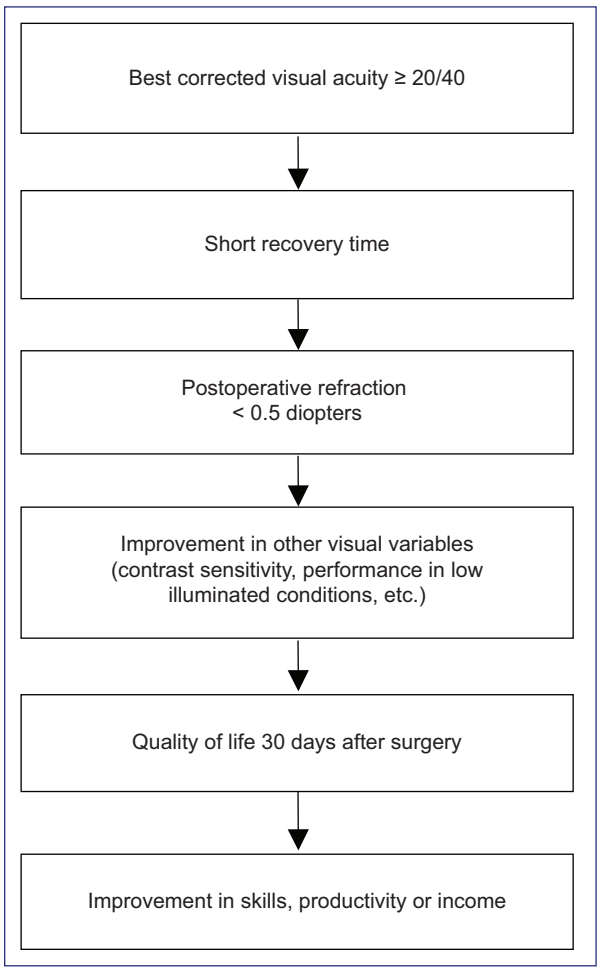

Figure 1. Proposed flowchart to evaluate quality in uncomplicated cataract surgery.

Economic considerations of quality after cataract surgery

The relevance of efficiency and quality rises as the cost of medical care does, and cataract surgery is cost-effective, compared to other ophthalmic and non-ophthalmic procedures. The waiting time for surgery is a factor that needs evaluation, because of the impact that visual impairment has on society;[45] although visual results do not change between patients undergoing early or delayed surgery,[46] the economic impact of deferral is unknown.[47]

Increasing the number of procedures, which is also a cost-effective intervention, balances the cost incurred in reducing surgical waiting time;[48] in a study from Nigeria, over 90% of patients who had cataract surgery reported that their skills, productivity, and income had increased after the procedure.[49] Cataract surgery in the first eye is cost-effective to prevent falls; surgery of the second eye does not add benefit regarding this topic.[48]

Concerning surgical complications, a posterior capsule tear increased post-operative visits to a mean 2.7 with the surgeon and three with other sub-specialists; mean surgical time rose to 61.4 min, which augmented the cost of the procedure. The need for other procedures and imaging studies also augments the cost of care.[50]

From a Social Return on Investment point of view, a Mexican study found that the independence gained by patients after cataract surgery also extends benefits to their caregivers, who can potentially enroll in other productive activities.[51] There is still a need for cost-utility studies in our country that address the outcome of cataract surgery in quality-adjusted life years.

Quantity versus quality

Learning phacoemulsification surgery requires about eighty complete procedures to achieve the basic

competency level; the best level requires more than three hundred.[52] Skilled cataract surgeons need to be prepared for anticipating, preventing, and solving intraoperative complications.

In a study of four million cataract surgeries, surgeons did a mean 335 procedures per year; a larger number of surgeries reduced the exposure to adverse events, but without a clinical difference.[53] A study with 4,028 cases did not find an association between surgical volume and posterior capsule tears.[54]

A Swedish study reported that surgical volumes below 400 procedures per year associate with posterior capsule tears in a multivariate analysis ($p < 0.001$, $B = 0.053$); however, the estimated odds ratio did not show a clinical difference (1.738, 95% confidence intervals 1.492-2.025).[55]

Conclusion

Assessing quality in cataract surgery requires a stepwise approach, starting with the visual result; an indicator of the proportion of patients whose visual result is ≥ 20/40, reported in every institution periodically, would produce relevant information about the efficacy of the intervention. The information of that indicator could help to assess other dimensions of quality, and help to improve the standard of care, both in ambulatory surgery and in massive interventions.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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BRIEF REVIEW

CRISPR/Cas9 in clinical practice: opportunities and challenges for Mexico

CRISPR/Cas9 en la práctica clínica: oportunidades y desafíos para México

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Abstract

CRISPR/Cas9 has moved from a gene-editing platform used in experimental biology to a clinically relevant therapeutic technology with approved and investigational applications in hematologic, hepatic, ophthalmologic, and cardiometabolic diseases. The objective of this brief review is to provide a clinically oriented synthesis of current CRISPR/Cas9-based therapies, summarize key efficacy and safety considerations, and discuss the translational requirements for implementation in Mexico and Latin America. A focused literature review was conducted using clinical-trial registries and peer-reviewed reviews of clinical translation, with emphasis on therapies that have reached human studies, approved products, pre-treatment testing, follow-up needs, and the Mexican institutional context. The available evidence shows that ex vivo editing for hemoglobinopathies has already reached regulatory approval, while in vivo editing programs such as NTLA-2001 and ocular CRISPR therapies remain in active clinical development. However, broad adoption in routine practice remains constrained by off-target risk assessment, immune and long-term safety monitoring, manufacturing complexity, and the need for multidisciplinary oversight. In Mexico, recent developments at UNAM, the Instituto Nacional de Pediatría, and IPN suggest growing technical capacity, but clinical translation will require coordinated regulatory, bioethical, laboratory, and referral frameworks. CRISPR/Cas9 should therefore be understood not as a universal intervention, but as a disease-specific therapeutic platform whose safe implementation depends on genotype confirmation, pre-treatment testing, structured follow-up, and institutional readiness.

Keywords: *CRISPR/Cas9. Gene editing. Clinical translation. Mexico. Genomic medicine. Cell and gene therapy.*

Resumen

CRISPR/Cas9 ha evolucionado de una plataforma de edición genética utilizada en biología experimental a una tecnología terapéutica clínicamente relevante con aplicaciones aprobadas y en investigación en enfermedades hematológicas, hepáticas, oftalmológicas y cardiometabólicas. El objetivo de esta breve revisión es proporcionar una síntesis clínicamente orientada de las terapias actuales basadas en CRISPR/Cas9, resumir las consideraciones clave sobre eficacia y seguridad, y analizar los requisitos de traslación para su implementación en México y Latinoamérica. Se realizó una revisión bibliográfica específica utilizando registros de ensayos clínicos y revisiones por pares de traslación clínica, con énfasis en terapias que han llegado a estudios en humanos, productos aprobados, pruebas previas al tratamiento, necesidades de seguimiento y el contexto institucional mexicano. La evidencia disponible muestra que la edición ex vivo para hemoglobinopatías ya ha alcanzado la aprobación regulatoria, mientras que los programas de edición in vivo, como NTLA-2001 y las terapias CRISPR oculares, se encuentran en desarrollo clínico activo. Sin embargo, su adopción generalizada en la práctica clínica habitual sigue limitada

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por la evaluación de riesgos fuera del objetivo, la monitorización inmunológica y de seguridad a largo plazo, la complejidad de la fabricación y la necesidad de supervisión multidisciplinaria. En México, los recientes avances en la UNAM, el Instituto Nacional de Pediatría y el IPN sugieren una creciente capacidad técnica, pero la traslación clínica requerirá marcos regulatorios, bioéticos, de laboratorio y de derivación coordinados. Por lo tanto, CRISPR/Cas9 debe entenderse no como una intervención universal, sino como una plataforma terapéutica específica para enfermedades cuya implementación segura depende de la confirmación del genotipo, las pruebas previas al tratamiento, el seguimiento estructurado y la preparación institucional.

Palabras clave: *CRISPR/Cas9. Edición de genes. Traducción clínica. México. Medicina genómica. Terapia celular y genética.*

Introduction

CRISPR/Cas9 has transformed biomedical research because it enables targeted DNA modification with a flexibility that accelerated the transition from experimental editing to clinical development.[1,2] Compared with earlier programmable nuclease platforms such as zinc-finger nucleases and TALENs, CRISPR/Cas9 is easier to retarget because specificity is mainly defined by guide RNA design rather than by engineering a new protein for each locus, which has facilitated broader adoption in research and therapeutic development.[1,2] In clinical practice, this transition became especially visible after the approval of exagamglogene autotemcel (exa-cel; Casgevy), an *ex vivo* CRISPR/Cas9 therapy targeting the BCL11A erythroid enhancer for sickle cell disease and transfusion-dependent β-thalassemia.[3,4]

The clinical relevance of CRISPR/Cas9 now extends beyond proof-of-concept. Ongoing programs include *in vivo* editing for transthyretin amyloidosis, ocular editing for CEP290-associated Leber congenital amaurosis, and other genome-editing approaches for hematologic and cardiometabolic disorders.[4-6] For clinicians, the practical question is no longer whether CRISPR can edit human cells, but which patients may benefit, what testing is required before treatment, how outcomes should be monitored, and what institutional safeguards are needed for implementation.[7,8]

These questions are particularly relevant in Mexico. The country has emerging academic and translational capacity in genome editing, including work at UNAM and the Instituto Nacional de Pediatría on monogenic diseases such as sickle cell disease and β-thalassemia, the creation of the Unidad de Edición Genética y Criopreservación at the Instituto de Fisiología Celular of UNAM, and gene-editing research at IPN aimed at disrupting CCR5-related HIV entry pathways.[9,10] At the same time, clinical implementation remains limited by regulatory complexity, infrastructure requirements, funding constraints, and the need for multidisciplinary governance.[11,12] This brief review, therefore, focuses on CRISPR/Cas9 as a clinical innovation and examines its therapeutic evidence, safety, pre-treatment evaluation, follow-up requirements, and implementation challenges in Mexico.

CRISPR/Cas9: prokaryotic origins and molecular mechanism

CRISPR/Cas systems originated as adaptive immune mechanisms in bacteria and archaea, where guide RNAs direct nuclease activity against foreign genetic material.[2] In the most commonly used CRISPR/Cas9 configuration, the single-guide RNA hybridizes with the complementary target DNA sequence adjacent to a protospacer adjacent motif, and Cas9 induces a double-strand break that can then be repaired by non-homologous end joining or homology-directed repair.[2,7] From a therapeutic perspective, this mechanism underlies both *ex vivo* strategies, in which cells are edited outside the body and reinfused, and *in vivo* strategies, in which editing components are delivered directly to target tissues[4,5] (Fig. 1).

Methods

A focused review of the literature was performed using peer-reviewed publications and clinical-trial registries that addressed CRISPR/Cas9 in human therapeutics, with emphasis on clinically relevant programs and translational considerations.[1,4,5] Sources included ClinicalTrials.gov, recent reviews of clinical trials, and publications addressing off-target assessment, long-term safety, and regional implementation issues.[5,7,8] The review prioritized studies and reports describing approved or investigational therapies, disease targets, treatment modality, clinical outcomes, safety considerations, and implications for implementation in Mexico and Latin America.[5,3,4]

The review question was pragmatic rather than PICO-based: which CRISPR/Cas9 therapies are closest to clinical practice, what efficacy and safety data

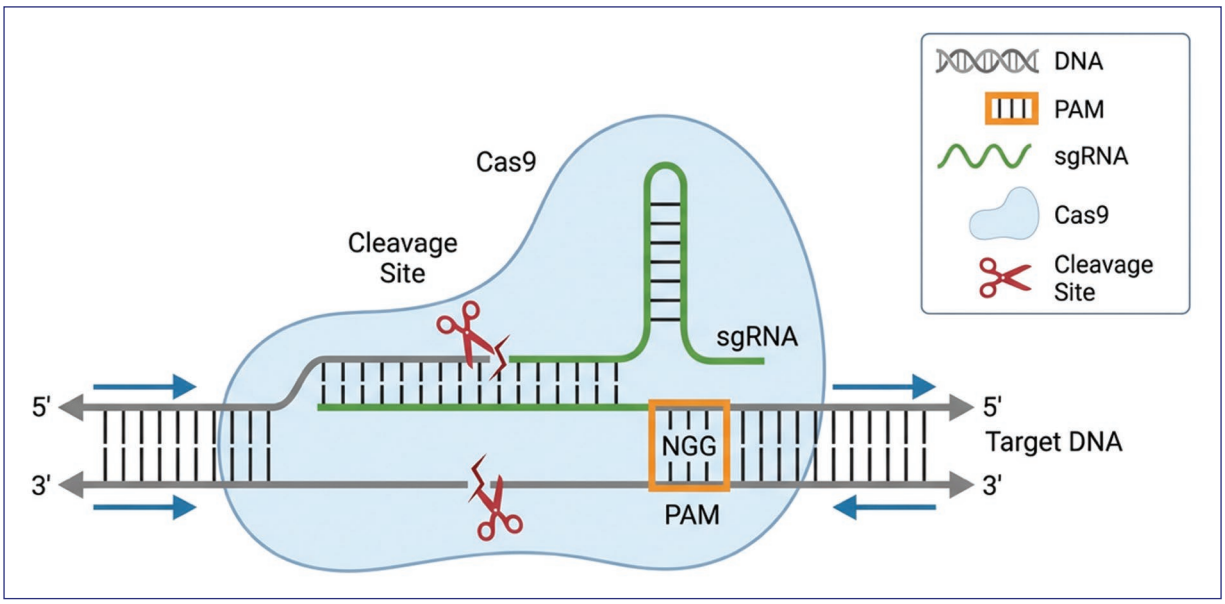

Figure 1. Molecular basis of CRISPR/Cas9 therapy: target gene, protospacer adjacent motif, single-guide RNA hybridization region, and Cas9 cleavage site.

are currently available, and what conditions are required for responsible implementation in Mexico.[1,7,8] Because the goal of the manuscript was a clinically oriented brief review rather than a formal systematic review, the search was designed to identify representative and high-impact translational evidence instead of exhaustively capturing all preclinical reports.[1,2]

Results

Included evidence and clinical scope

Fifteen core sources were selected for detailed synthesis because they provided direct information on approved products, active clinical programs, safety evaluation, or the Mexican institutional context of CRISPR translation.[1-15] The included evidence covered approved *ex vivo* editing for hemoglobinopathies, *in vivo* hepatic editing, ocular editing, preclinical and clinical safety assessment, and translational infrastructure relevant to Mexico[3-5,7] (Table 1).[1,3-13,15-17]

Disease-specific clinical applications

The most advanced clinical application of CRISPR/Cas9 is exagamglogene autotemcel (exa-cel; Casgevy), an *ex vivo* therapy in which autologous hematopoietic stem and progenitor cells are edited at the BCL11A erythroid enhancer to increase fetal hemoglobin and reduce the clinical burden of sickle cell disease and transfusion-dependent β-thalassemia.[3,4,15] This program represents a major translational milestone because it established that genome editing can move beyond experimental hematology and into regulatory approval.[3,6]

Other CRISPR programs remain under active investigation. NTLA-2001 is an *in vivo* CRISPR/Cas9 therapeutic targeting TTR for hereditary transthyretin amyloidosis and has been studied as an open-label dose-escalation and expansion program designed to characterize safety, pharmacodynamics, and initial clinical activity.[4,5] Ocular editing has also reached human studies through EDIT-101 for CEP290-associated Leber congenital amaurosis type 10, demonstrating the feasibility of local *in vivo* delivery in ophthalmology.[3,4] Beyond these programs, the broader clinical pipeline includes additional hematologic and cardiometabolic editors, including investigational approaches that target pathways such as PCSK9 or ANGPTL3 to reduce atherogenic lipoproteins[6,16] (Table 2).[3-6,16]

Pre-treatment evaluation and candidate selection

CRISPR/Cas9 cannot be considered a universal therapeutic option because efficacy and risk depend on the specific disease, target tissue, editing strategy, and patient genotype.[7,8] Before treatment, clinicians should confirm

Table 1. Summary of the 15 core sources included in the review, with study type, disease area, intervention or topic, and principal clinical or translational findings

Source	Type	Disease area/topic	Intervention or focus	Principal findings relevant to clinical practice
ClinicalTrials.gov NCT04601051[5]	Trial registry	Hereditary transthyretin amyloidosis	NTLA-2001, *in vivo* CRISPR/Cas9 targeting TTR	Ongoing first-in-human program assessing safety, PK/PD, and clinical activity
Review of current CRISPR therapeutics[16]	Review	Hematology/broader pipeline	BEAM-101, EDIT-101, EDIT-301 and others	Highlights expanding clinical pipeline beyond exa-cel
Gene therapy clinical overview[6]	Clinical review	Hemoglobinopathies, cardiometabolic disease	Casgevy, Verve-101/102	Summarizes approval milestone and emerging cardiovascular editing programs
Delivery and therapeutic pipeline review[3]	Review	Multiple	Exa-cel, NTLA-2001, EDIT-101	Confirms approved and phase-specific programs
Selected clinical trials table[4]	Trial summary	Multiple	Exa-cel, NTLA-2001, EDIT-101	Provides concise mapping of current clinical-stage genome-editing therapies
Clinical trends review[1]	Review	Multiple	CRISPR/Cas clinical trials	Describes global trends and therapeutic directions
Off-target assessment review[7]	Safety review	Multiple	Off-target assays and risk assessment	Summarizes methods for preclinical and translational off-target evaluation
Frontiers off-target review[13]	Safety review	Multiple	Regulatory relevance of off-target testing	Supports structured preclinical safety evaluation
Clinical interpretation of off-targets[8]	Perspective	Multiple	Benefit-risk interpretation of off-target events	Emphasizes clinical risk assessment framework
β-globin CRISPR strategy review[15]	Review	Sickle cell disease/ β-thalassemia	BCL11A/HbF pathway	Relevant for genotype-specific therapeutic rationale
β-globin therapeutic review[17]	Review	β-hemoglobinopathies	Gene-editing strategies	Discusses disease biology and target-pathway considerations
Mexican regulation review[11]	Regulatory resource	Mexico	Clinical research governance	Details role of COFEPRIS, ethics, and research committees
Mexico regulation tracker[12]	Policy resource	Mexico	Therapeutic/stem-cell regulation	Supports national regulatory context
IPN CCR5 report[9]	Institutional report	HIV-related experimental editing	CRISPR editing of CCR5/CXCR4 pathways	Shows local genome-editing capability and translational expertise
UNAM clinical/ genome-editing reports[10]	Institutional/ science communication	Mexico	Human clinical entry and academic development	Illustrates national academic engagement in CRISPR translation

the molecular diagnosis using validated genetic testing and define whether the patient's disease biology matches the therapeutic target, as is particularly important in hemoglobinopathies where the rationale of therapy depends on the HBB/BCL11A/HbF regulatory axis.[15,17] In this context, it is more accurate to discuss genetic variants as potential modifiers of response rather than to attribute treatment failure vaguely to "genetic heterogeneity".[15,17]

A baseline evaluation should also include disease-severity assessment, organ-function testing, and modality-specific safety screening. For *ex vivo* hematopoietic editing, this includes complete blood count, hemolysis markers when relevant, renal and hepatic function, infectious screening, transfusion history, and assessment of eligibility for stem-cell mobilization, myeloablative conditioning, and reinfusion.[6,7] For *in vivo* editing

Table 2. Approved and investigational CRISPR-based therapies of greatest clinical relevance, including target, modality, phase, principal outcomes, and implications for long-term follow-up

Therapy/ program	Target	Indication	Modality	Clinical stage	Main reported outcome	Key follow-up need
Exagamglogene autotemcel (Casgevy)[3,4]	*BCL11A* erythroid enhancer	Sickle cell disease; transfusion-dependent β-thalassemia	*Ex vivo* CRISPR/Cas9	Approved/ phase 2-3 completed	Clinically meaningful disease-control benefit through HbF induction	Long-term durability, secondary malignancy surveillance, transplant-related follow-up
NTLA-2001[4,5]	*TTR*	Hereditary transthyretin amyloidosis	*In vivo* CRISPR/ Cas9	Phase 1; phase 3 ongoing	Ongoing evaluation of safety, PK/PD, and clinical measures	Hepatic monitoring, long-term genomic safety, durability
EDIT-101[3,4]	*CEP290* IVS26 mutation	Leber congenital amaurosis type 10	*In vivo* CRISPR/ Cas9, subretinal	Phase 1/2	Demonstrates translational feasibility of ocular editing	Ocular functional follow-up and retinal safety
EDIT-301[16]	HbF pathway	Sickle cell disease/ severe hemoglobinopathies	*Ex vivo* genome editing	Clinical development	Expanding pipeline in hematology	Long-term engraftment and hematologic safety
BEAM-101[16]	Fetal hemoglobin regulatory strategy	Sickle cell disease	*Ex vivo* editing	Clinical development	Broader next-generation editing pipeline	Durability and comparative effectiveness
Verve-101/ Verve-102[6]	*PCSK9* pathway	Hypercholesterolemia/ cardiometabolic risk	*In vivo* base-editing platform	Early clinical development	Marked LDL-C lowering reported in early studies	Cardiovascular event monitoring and off-target risk interpretation

Table 3. Recommended pre-treatment tests and baseline evaluations before CRISPR/Cas9 therapy, according to the clinical use scenario

Clinical scenario	Recommended baseline tests/evaluations	Main purpose
Ex vivo hematopoietic editing for sickle cell disease or β-thalassemia[6,15]	Molecular diagnosis confirmation, CBC, reticulocytes, bilirubin/ LDH, ferritin, renal and liver function, transfusion history, infectious screening, cardiopulmonary evaluation, fertility counseling as appropriate	Confirm indication, assess disease burden, determine transplant/ conditioning fitness
In vivo hepatic editing (e.g., TTR programs)[5,7]	Molecular confirmation, liver profile, renal function, disease biomarkers, neurological/cardiac baseline depending on indication, concomitant medication review	Confirm target disease, establish PD and safety baseline
Ocular CRISPR therapies[3,4]	Molecular diagnosis, ophthalmologic imaging, and visual-function testing, mutation-specific eligibility confirmation	Verify targetable mutation and baseline functional status
Any CRISPR therapeutic candidate[7,8]	Benefit-risk review, informed consent, counseling on long-term uncertainty, and institutional multidisciplinary review	Improve selection, consent quality, and safety governance

programs, pre-treatment workup should incorporate target-organ assessment and biomarker baselines that allow efficacy and adverse-event monitoring over time[5,7,8] (Table 3).[3-8,15]

Safety considerations and monitoring

A clinically meaningful discussion of CRISPR/Cas9 must include safety. The most important concerns are

off-target edits, large genomic rearrangements or structural variants at or near edited loci, immune responses to editing components or delivery vehicles, and uncertain long-term risk, particularly in permanently edited cells.[7,8,13] The literature emphasizes that off-target assessment should combine *in silico* prediction, biochemical or cell-based assays, and locus-specific confirmatory approaches, because no single method fully captures clinical risk.[7,13]

For this reason, the quality of preclinical off-target evaluation and long-term follow-up should be viewed as part of the therapeutic package, not as an optional add-on.[7,8] In practice, long-term monitoring should include disease-specific efficacy outcomes, hematologic or organ-specific adverse events, surveillance for delayed complications, and documentation in structured follow-up programs capable of capturing rare or late toxicities.[6,8]

CRISPR/Cas9 research and implementation capacity in Mexico

Mexico has a growing, though still preclinical and translationally uneven, CRISPR ecosystem. UNAM and the Instituto Nacional de Pediatría have used CRISPR to study monogenic diseases, including sickle cell disease and β-thalassemia, while the Unidad de Edición Genética y Criopreservación created at the Instituto de Fisiología Celular of UNAM, provides transgenic-animal and cryopreservation services to researchers from UNAM and other public and private universities, health institutes, and industry.[10] This type of infrastructure is highly relevant because therapeutic translation requires not only conceptual expertise but sustained access to genome-editing platforms, quality control, biobanking, and specialized technical support.[10,11]

Additional examples reinforce the national capacity for translational development. At IPN, investigators have reported CRISPR/Cas9-based disruption of HIV entry-related coreceptor pathways such as CCR5, with marked reduction of CCR5 expression in edited cells in an experimental setting.[9] Although this work is not yet a clinical therapy, it demonstrates local expertise in guide design, gene editing, and molecular validation.[9] Outside human therapeutics, Mexican CRISPR work in agriculture, including CINVESTAV efforts to improve productivity and adaptation of native maize, further reflects national competence in genome-editing platforms, even when the translational path differs from clinical medicine.[10]

Institutional and regulatory framework needed in Mexico

The clinical use of CRISPR/Cas9 in Mexico will require a multidisciplinary governance structure. Nationally, the regulatory environment involves COFEPRIS, research committees, research ethics committees, and, where relevant, biosafety and specialized technical review mechanisms.[11,12] For high-complexity gene-editing therapies, an implementation committee should also incorporate expertise from genomic medicine, hematology or the relevant specialty, transplant medicine when applicable, molecular pathology, bioinformatics, pharmacovigilance, biostatistics, bioethics, and health-law or regulatory professionals.[8,11]

From an institutional standpoint, no single center is likely to provide all the capabilities required for candidate selection, manufacturing coordination, conditioning support, long-term follow-up, and adverse-event surveillance.[8,11] A realistic Mexican model would therefore involve a network linking academic centers with genome-editing capability, tertiary referral hospitals, transplant or advanced-therapy services, ethics and research bodies, and national regulatory authorities.[9-11]

Discussion

This review shows that CRISPR/Cas9 is no longer only an experimental technology; it is already part of clinical medicine in selected indications and is expanding through a heterogeneous therapeutic pipeline.[3-5] However, the current evidence also makes clear that clinical translation is disease-specific and modality-specific: *ex vivo* hematopoietic editing has reached the greatest maturity, whereas *in vivo* editing remains promising but still dependent on continued safety and durability data.[3,5,8]

The first major implication for clinicians is that efficacy claims should be described with sufficient specificity. It is not enough to state that CRISPR approaches are “promising”; the literature supports a more disciplined discussion focused on target pathway, clinical stage, observed outcomes, and the durability of benefit.[4-6] This is especially important in hemoglobinopathies, where the success of current therapeutic models is closely tied to reactivation of fetal hemoglobin through BCL11A-related editing.[3,15]

The second implication concerns patient selection. Reviewing CRISPR/Cas9 through the lens of “genetic heterogeneity” alone is too imprecise for clinical practice.[15,17] The more relevant issue is whether the patient’s

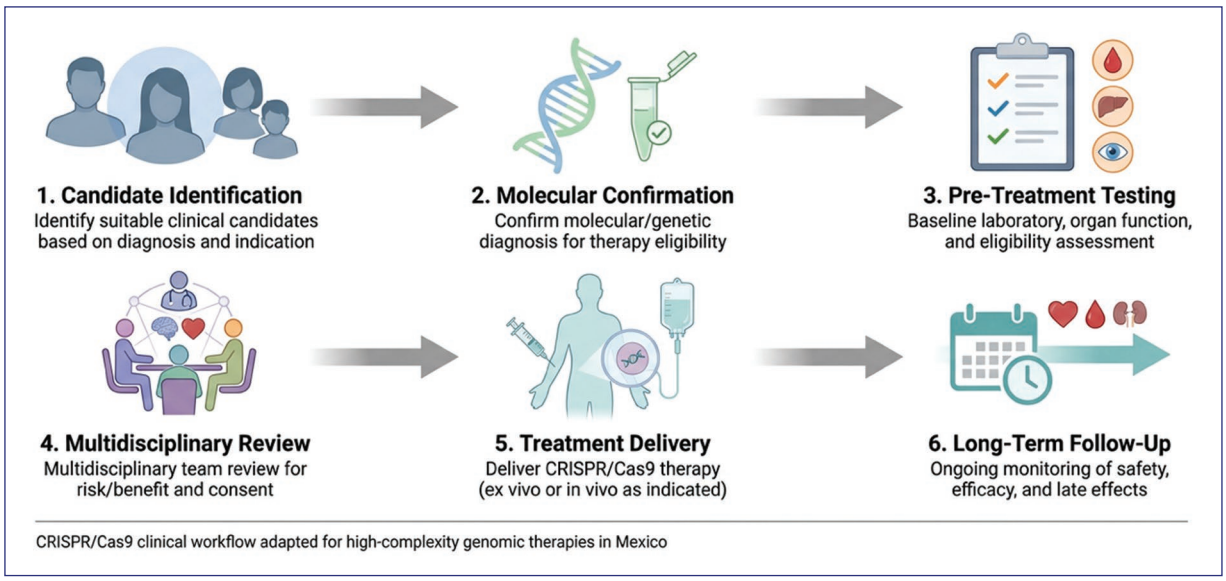

Figure 2. Clinical workflow for CRISPR/Cas9 therapy: candidate identification, molecular confirmation, pre-treatment testing, multidisciplinary review, treatment delivery, and long-term follow-up.

genotype, target biology, disease stage, and treatment context are appropriate for a given editing strategy, and whether baseline testing is sufficient to support both expected efficacy and safety surveillance.[7,8,15]

The third implication is that safety must remain central. Off-target effects, immune phenomena, genomic rearrangements, and delayed risks are not theoretical objections but core dimensions of benefit-risk assessment.[7,8] This supports the creation of formal follow-up groups or registries for edited patients, particularly for therapies that may have durable or irreversible genomic consequences.[8,14]

The Mexican context adds both opportunity and complexity. On the one hand, national institutions already demonstrate meaningful capacity in CRISPR research, including monogenic disease modeling, gene-editing infrastructure, and molecular validation workflows.[9,10] On the other hand, translation to clinical care will require sustained financing, manufacturing partnerships, trained personnel, referral pathways, regulatory clarity, and long-term outcome surveillance systems that are not yet routine in most Mexican health institutions.[11,12]

These findings support a practical framework for Mexico. Initial clinical adoption, if it occurs, will likely be concentrated in highly specialized centers and should be based on multidisciplinary case review, molecular confirmation of the indication, standardized pre-treatment testing, and registry-based longitudinal follow-up.[7,8,11] In that sense, CRISPR/Cas9 should be approached as a platform for precision therapeutics rather than as a universally deployable treatment (Fig. 2).

Conclusion

CRISPR/Cas9 has entered clinical practice through a limited but highly significant group of therapies, led by *ex vivo* editing for hemoglobinopathies and followed by an expanding pipeline of *in vivo* and organ-targeted programs.[3-5] Its clinical value depends not only on editing capacity but on rigorous patient selection, genotype-informed therapeutic rationale, pre-treatment testing, and long-term safety surveillance.[7,8,15] In Mexico, emerging academic and technical capacity at UNAM, the Instituto Nacional de Pediatría, and IPN provides a foundation for future translation, but responsible implementation will require coordinated regulatory oversight, institutional networks, and multidisciplinary follow-up structures.[9-11] The most realistic near-term role of CRISPR/Cas9 in Mexico is therefore as a high-complexity precision therapy delivered in selected centers under robust clinical, ethical, and regulatory governance.[8-11]

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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BRIEF COMMUNICATION

Wilms tumor in adults. Case report and literature review

Tumor de Wilms en el adulto. Reporte de un caso y revisión de la literatura

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Abstract

Wilms tumor is an extremely rare malignant neoplasm in adults, with approximately 300 cases described in this age group. Clinical outcomes are not as favorable as in children, although with the latest treatment protocols; long-term survival rates of approximately 82% have been reported. A 20-year-old woman presented with abdominopelvic pain, a palpable mass in her left flank, and pain in her right hip bone. A computed tomography scan revealed a tumor originating from the left kidney, metastases to the neck, lungs, liver, retroperitoneum, right acetabulum, and L1 vertebral body, and lymphadenopathy in the mediastinum, pulmonary hilum, and retroperitoneum. She underwent nephrectomy; the pathology report described a Wilms tumor with triphasic histology and diffuse anaplasia. She received treatment according to the UMBRELLA SIOP – Renal Tumor Study Group2016 protocol, regimen for tumors with anaplastic histology in the adult Wilms tumor treatment arm and initial nephrectomy. Disease progression occurred at week 16 of the protocol. The protocol was changed to vincristine-irinotecan and intermediate radiotherapy. The disease was stable after 5 weeks of treatment; however, she died from septic shock. Further clinical trials in adults with Wilms tumor are needed to define effective treatment guidelines.

Keywords: *Wilms tumor. Nephroblastoma. Kidney tumors. Renal cancer. Adult nephroblastoma. Cancer.*

Resumen

El tumor de Wilms es una neoplasia maligna extremadamente rara en adultos, habiéndose descrito alrededor de 300 casos en este grupo etario. Los resultados clínicos no son tan satisfactorios como en los niños, si bien con los últimos protocolos de tratamiento se han descrito supervivencias a largo plazo de aproximadamente el 82%. Mujer de 20 años con dolor abdominopélvico, tumor palpable en flanco izquierdo, y dolor en hueso coxal derecho. La tomografía evidenció un tumor dependiente del riñón izquierdo, metástasis a cuello, pulmones, hígado, retroperitoneo, acetábulo derecho y cuerpo vertebral de L1, y adenomegalias en mediastino, hilios pulmonares y retroperitoneo. Operada de nefrectomía; el reporte anatomopatológico describió un tumor de Wilms de histología trifásica y anaplasia difusa. Recibió tratamiento de acuerdo con el protocolo UMBRELLA SIOP-RTSG 2016, régimen para tumores con histología anaplásica del brazo de tratamiento para adultos con tumor de Wilms y nefrectomía inicial, con progresión de la enfermedad en la semana 16 del protocolo; cambio de protocolo a vincristina-irinotecán, y radioterapia intermedia, con enfermedad estable luego de 5 semanas de tratamiento, no obstante, falleció por choque séptico. Se requieren más ensayos clínicos en adultos con tumor de Wilms, para definir pautas terapéuticas eficaces.

Palabras clave: *Tumor de Wilms. Nefroblastoma. Tumores renales. Cáncer renal. Nefroblastoma en adultos. Cáncer.*

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Introduction

Wilms tumor, or nephroblastoma, is the most common kidney tumor in childhood, accounting for 7% of all childhood malignancies, with an incidence rate of approximately 9.7 cases/million children under 15 years of age per year (13.5/million infants per year),[1] a peak incidence at 44 months of age,[2] and significant ethnic variations, being less frequent in Asian individuals.[3]

Wilms tumor is an extremely rare malignancy in adults, with approximately 300 cases described in this age group since the tumor was first characterized (< 1% of adult kidney tumors, with a rate of 0.2 cases/million per year).[4-10]

A congenital anomaly is identified in approximately 9% of patients with Wilms tumor,[11] and a cancer predisposition syndrome is present in approximately 4.7% of cases.[12] Given the limited number of reported cases, the exact frequency of congenital anomalies in adults with Wilms tumor is unknown. However, data from exome sequencing of adult patients describe mutations in the *BRAF* gene in a significant proportion of cases, a gene that is not usually mutated in pediatric patients.[13]

Histologically, it is divided into Wilms tumor with favorable histology or anaplastic Wilms tumor. Wilms tumor with favorable histology may be composed of 1-3 cell elements (triphasic, so named because it is composed of three main cellular elements that mimic the embryonic development of the normal kidney, namely, blastema, epithelium, and stroma). Anaplasia, the presence of which is associated with a poor prognosis, is found in 10% of Wilms tumor cases (more frequent with increasing age at diagnosis). It is characterized by multipolar polyploid mitotic figures and hyperchromasia, and its presence is the main predictor of survival.[14,15]

The initial clinical presentation is characterized by an abdominal mass, hematuria, and hypertension, and in some cases, fever, anorexia, weight loss, abdominal pain, and clinical signs associated with pulmonary embolism, vascular compression, or hemorrhage.[15] The therapeutic approach is multimodal and is based on the clinical stage, histological type, and loss of heterozygosity at 1p/16q[16] (loss of alleles of tumor suppressor genes located in said chromosomal regions).

Disease-free survival for this neoplasm has been increasing with successive multimodal treatment protocols; in pediatric patients, by 1975, the 5-year survival rate was around 80%, currently reaching approximately 93%.[17,18] In the case of Wilms tumor in adults, clinical outcomes are not as satisfactory as in children, although with the latest treatment protocols, long-term survival rates of approximately 82.6% have been reported.[18]

Most clinical trials on the treatment of Wilms tumors have been conducted by two major working groups: the Children's Oncology Group (COG) of North America and the International Society of Paediatric Oncology (SIOP). The COG performs initial surgery (nephrectomy or biopsy) as the first approach for patients with unilateral renal tumors, while the SIOP uses neoadjuvant chemotherapy without initial biopsy. Both groups use adjuvant chemotherapy when required by the patient's clinical stage.[19,20]

Initial surgery allows for early histological diagnosis; however, it increases the risk of tumor spillage and reduces the likelihood of achieving lower post-operative stages. In contrast, initial chemotherapy significantly alters the tumor's histological characteristics, making blastemic and mixed histological types less, with the possibility eliminating diffuse anaplasia and decreasing the proportion of Stage III cases.[19,20]

Both the COG and SIOP recommend consulting a pediatric oncologist as soon as Wilms tumor is diagnosed in an adult.[21]

We report this case of Wilms tumor due to its low frequency in adulthood, highlighting the minimal diagnostic suspicion and the poor therapeutic response to the treatment protocols used.

Case report

A 20-year-old woman presented with intermittent abdominopelvic pain, which became severe, a palpable mass in her left flank, and pain in her right hip bone, of 2 months' duration. Initial computed tomography (CT) scan revealed an 18.5 cm left kidney tumor with metastases to the neck, lungs, liver, retroperitoneum, right acetabulum, and L1 vertebral body (with a compression fracture), and lymphadenopathy in the mediastinum, pulmonary hilum, and retroperitoneum (Figs. 1 and 2).

A left nephrectomy was performed 1 month after her initial consultation; the histopathological study reported a Wilms tumor with triphasic histology and diffuses anaplasia (Fig. 3). It is classified as clinical Stage IV according to the SIOP protocol, due to the presence of distant metastases. Initially, radiotherapy was administered to the right hip bone for local pain control. Chemotherapy was initiated 3 weeks post-surgery according to the 2016 UMBRELLA SIOP- Renal Tumor Study Group (RTSG) protocol of the RTSG of the SIOP,

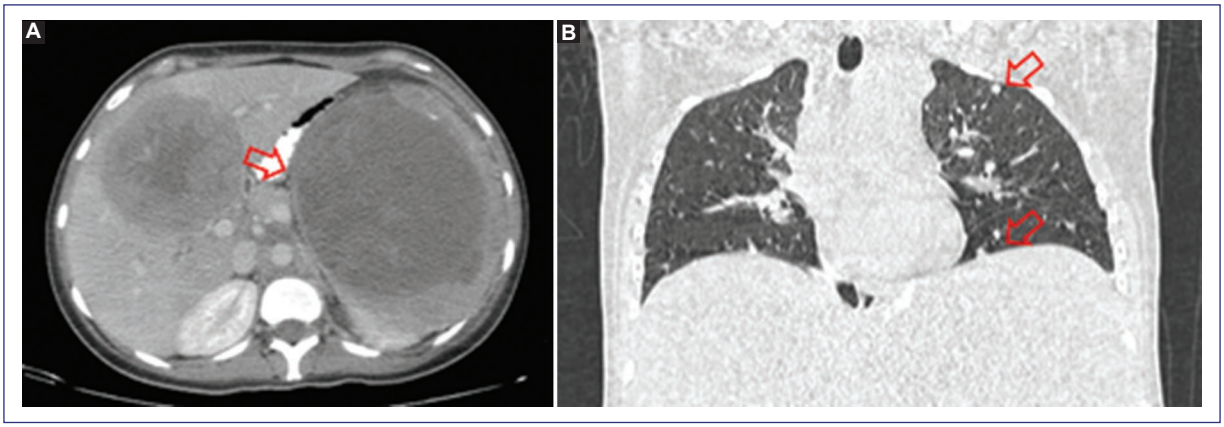

Figure 1. Computed tomography showing on **A:** axial section, a tumor arising from the left kidney measuring 18.5 × 14.6 × 13.3 cm in its greatest dimensions (arrow); a hepatic metastasis is also visualized. **B:** pulmonary metastases are identified in the left apical and basal regions (arrows).

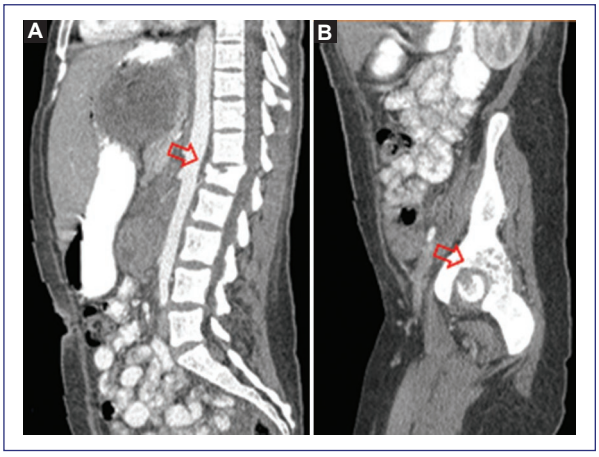

Figure 2. Sagittal computed tomography showing. **A:** metastasis to the L1 vertebral body with compression fracture (arrow), and **B:** metastasis to the right acetabulum with cortical destruction and a permeative pattern (arrow).

using the regimen for tumors with anaplastic histology from the treatment arm for adults with Wilms tumor and initial nephrectomy; the term "umbrella" is used due to the protocol's methodological design, which evaluates multiple chemotherapy regimens.

Over the course of 5 months, 16 weeks of the protocol were administered (3 cycles of course 1 [cyclophosphamide-doxorubicin], alternating with 3 cycles of course 2 [etoposide-carboplatin]), with delays between cycles of up to 2 weeks due to Grade 3 or 4 hematologic toxicity. Radiotherapy was initiated in the 3rd cycle (week 4 of the protocol), targeting only the surgical site and abdomen, with the lungs and neck planned to be irradiated in a second period to avoid broad radiation fields.

A partial response was obtained in the abdomen and a stable response in the thorax in interim CT scans.

After week 16 of the protocol, disease progression was observed in the lungs, and metastases were found in the skull and brain, accompanied by subarachnoid and intraparenchymal hemorrhage of the left parietal lobe and status epilepticus (Fig. 4); the treatment protocol was changed to vincristine-irinotecan.

The patient received 3 weeks of vincristine, alternating with 2 weeks of vincristine-irinotecan, administered weekly without delays, and concomitant radiotherapy to the head and lungs. The disease was stable as assessed by CT scan; however, the patient developed septic shock refractory to intensive treatment without an evident infectious focus and died as a result of the infection, having survived for 8 months from the time of diagnosis (Fig. 5).

Discussion

There is no screening method for renal tumors in children or adults, so these neoplasms are commonly diagnosed at advanced clinical stages. This, coupled with non-specific clinical manifestations, appears to be the main reason for the limited diagnosis in early clinical stages, rather than limitations in diagnostic and therapeutic resources.

We present the case, highlighting the high tumor burden and the site of metastases at the time of

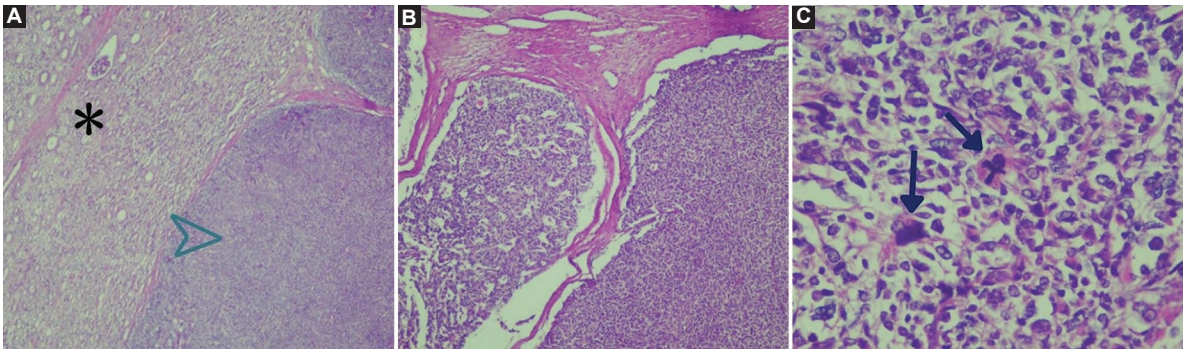

Figure 3. **A:** residual renal parenchyma (*) infiltrated by blastema (arrow) is observed. **B:** epithelial component characterized by tubular formation (left), blastema (right), and stromal component (top). **C:** anaplastic cells are shown, characterized by enlarged size and multipolar mitotic figures (arrows).

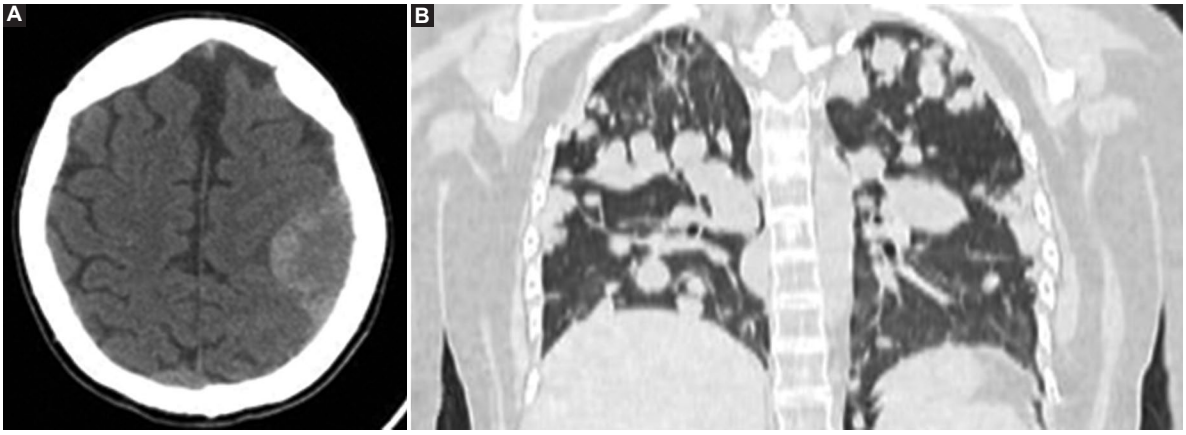

Figure 4. Computed tomography demonstrating. **A:** subarachnoid and intraparenchymal hemorrhage in the left parietal lobe and. **B:** progression of the disease in lungs.

diagnosis, as well as the presence of diffuse anaplasia, features observed in only a minority of reported cases, which led to an unfavorable clinical course.

The diagnosis of Wilms tumor was established by the location of the primary tumor, as well as by the histopathological characteristics obtained through routine hematoxylin and eosin staining, and by compatible immunohistochemistry.

The multidisciplinary team decided to offer treatment according to the SIOP protocol, as it includes a specific arm for adult patients with Wilms tumor.

The patient initially underwent a nephrectomy because the diagnosis of Wilms tumor was not suspected due to her age group. She also received radiotherapy to the hip bone for pain control (off-protocol), with a good response.

Next-generation sequencing and detection of loss of heterozygosity on chromosomes 1p/16q were not performed. At our institution, these studies are reserved for patients without other poor prognostic factors, in order to optimize resources, and are only performed in patients for whom an unfavorable result would alter the treatment plan.

During initial staging, magnetic resonance imaging was not used to assess the potential presence of metastases to the central nervous system due to the low suspicion of metastasis to that site. Initially, adverse factors identified included high tumor burden, the sites and number of metastases, nutritional status and

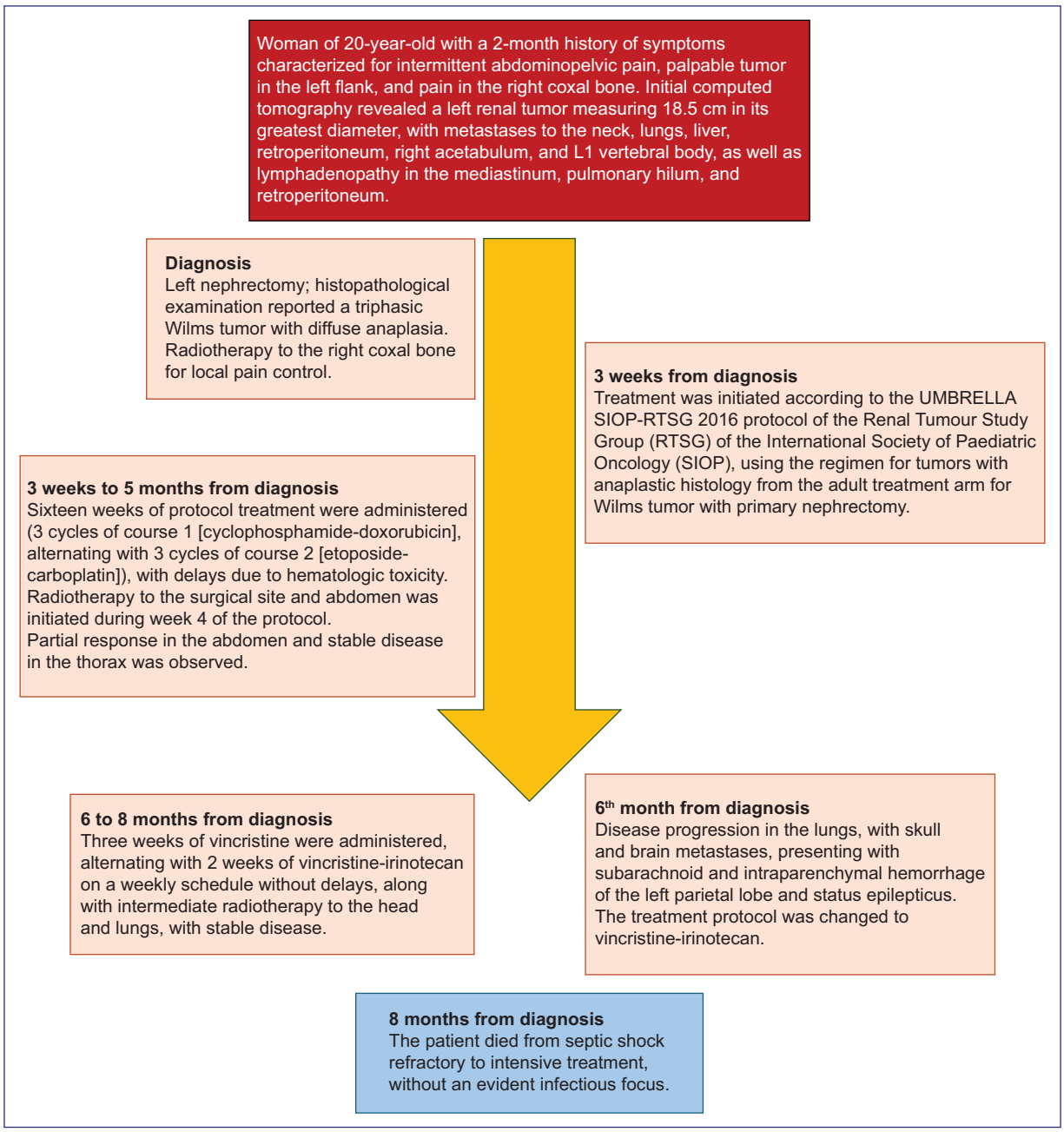

Figure 5. Chronological sequence of the clinical evolution.

functional class, as well as diffuse anaplasia on histopathological examination.

Although the patient initially showed a significant response, as assessed clinically and by CT scan, the disease progressed after week 16 of the initial protocol, suggesting apparent resistance to the cytotoxic therapy employed.

The protocol was changed to vincristine-irinotecan, and the patient's disease was stable. However, she died from sepsis associated with the antineoplastic treatment.

It is worth noting that the pancytopenia observed during the sepsis episode (which culminated in the patient's death) included profound neutropenia, a finding that is uncommon for the type of chemotherapy administered. Our medical team identifies the extensive radiation fields used and potential bone marrow infiltration as factors that may have contributed to this adverse

reaction. Although bone marrow infiltration was not investigated due to its rarity, we now believe it should have been assessed, given the high tumor burden and the presence of bone metastases.

In retrospect, we believe that next-generation sequencing could have been appropriate to identify a therapeutic target.

In two large published case series of adults with Wilms tumor, metastatic disease was present in 33.3% and 40.7% of cases (Stage IV); likewise, anaplasia was reported in 6.6% and 14.8% of cases, respectively, representing a factor associated with a very poor prognosis during the clinical course.[22,23] Most recent case reports and case series regarding Wilms tumor in adults describe the presence of distant metastases and anaplasia in fewer than half of the patients.

Further studies are needed to increase the clinical evidence of the efficacy of the chemotherapy used, with the aim of establishing better-defined therapeutic guidelines for adult patients with Wilms tumor as a result of future clinical trials.[18-20]

The discrepancies in disease-free survival between pediatric and adult patients with Wilms tumor could be due to biological differences in sensitivity to radiotherapy and cytotoxic drug therapy, although the influence of social factors or clinical decisions made by physicians based on the patient's functional status, which is usually given considerable weight by adult oncologists, cannot be ruled out.[21]

The Research Ethics Committee of the Juárez Hospital in Mexico City granted a full waiver of consent due to the retrospective nature of the study, in accordance with current Mexican law.

Conclusion

Further clinical trials in adults with Wilms tumor are needed to define effective treatment guidelines.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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